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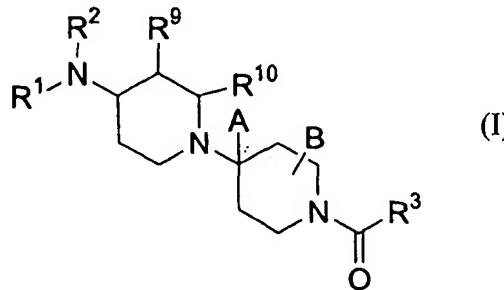
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(54) Title: PIPERIDINE DERIVATIVES USEFUL AS CCR5 ANTAGONISTS

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(57) Abstract: The present invention provides a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein R¹, R², R³, R⁹, R¹⁰, A and B are as defined in the specification. The present invention also provides pharmaceutical compositions containing the compound of this invention, and methods of treatment using the compound of this invention. The invention also relates to the use of a combination of a compound of this invention and one or more antiviral or other agents useful in the treatment of Human Immunodeficiency Virus (HIV). The invention further relates to the use of a compound of this invention, alone or in combination with another agent, in the treatment of solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid

arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis.

PIPERIDINE DERIVATIVES USEFUL AS CCR5 ANTAGONISTS**CROSS REFERENCE TO RELATED APPLICATION**

5 This application claims priority to U.S. Provisional Application
60/315683, filed August 29, 2001.

FIELD OF INVENTION

10 The present invention relates to piperidine derivatives useful as
selective CCR5 antagonists, pharmaceutical compositions containing the
compound of this invention, and methods of treatment using the inventive
compounds. The invention also relates to the use of a combination of the
compound of this invention and one or more antiviral or other agents useful
15 in the treatment of Human Immunodeficiency Virus (HIV). The invention
further relates to the use of the compound of this invention, alone or in
combination with another agent, in the treatment of solid organ transplant
rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory
bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple
20 sclerosis.

BACKGROUND OF INVENTION

The global health crisis caused by HIV, the causative agent of
Acquired Immunodeficiency Syndrome (AIDS), is unquestioned. While
25 recent advances in drug therapies have been successful in slowing the
progression of AIDS, there is still a need to find a safer, more efficient, less
expensive way to control the virus.

It has been reported that the CCR5 gene plays a role in resistance to
HIV infection. HIV infection begins by attachment of the virus to a target
30 cell membrane through interaction with the cellular receptor CD4 and a
secondary chemokine co-receptor molecule, and proceeds by replication
and dissemination of infected cells through the blood and other tissue.
There are various chemokine receptors, but for macrophage-tropic HIV,
believed to be the key pathogenic strain that replicates *in vivo* in the early

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stages of infection, the principal chemokine receptor required for the entry of HIV into the cell is CCR5. Therefore, interfering with the interaction between the viral receptor CCR5 and HIV can block HIV entry into the cell. The present invention relates to small molecules which are CCR5 antagonists.

CCR5 receptors have been reported to mediate cell transfer in inflammatory diseases such as arthritis, rheumatoid arthritis, atopic dermatitis, psoriasis, asthma and allergies. Inhibitors of such receptors are expected to be useful in the treatment of such diseases, and in the treatment of other inflammatory diseases or conditions such as inflammatory bowel disease, multiple sclerosis, solid organ transplant rejection and graft v. host disease.

Other piperidine derivatives, which are muscarinic antagonists useful in the treatment of cognitive disorders such as Alzheimer's disease, are disclosed in US patents 5,883,096, 6,037,352, 5,889,006, 5,952,349, and 5,977,138.

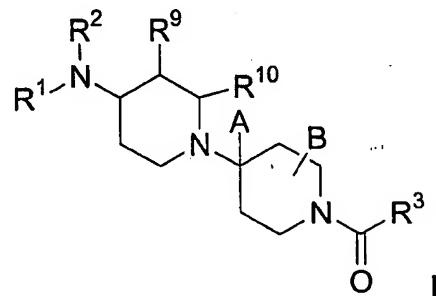
A-M. Vandamme et al., Antiviral Chemistry & Chemotherapy, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections in man including at least triple drug combinations or so-called Highly Active Antiretroviral Therapy ("HAART"). HAART involves various combinations of nucleoside reverse transcriptase inhibitors ("NRTI"), non-nucleoside reverse transcriptase inhibitors ("NNRTI") and HIV protease inhibitors ("PI"). In compliant drug-naive patients, HAART is effective in reducing mortality and the progression of HIV-1 to AIDS. However, these multidrug therapies do not eliminate HIV-1 and long-term treatment usually results in multidrug resistance. Development of new drug therapies to provide better HIV-1 treatment remains a priority.

SUMMARY OF THE INVENTION

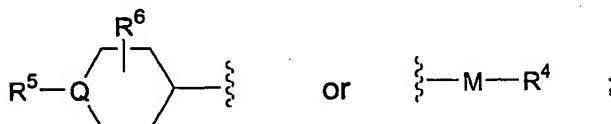
The present invention provides a novel class of compounds as antagonists of the CCR5 receptor, methods of preparing such compounds, pharmaceutical compositions containing one or more such compounds, and methods of treatment, prevention or amelioration of one or more diseases associated with the CCR5 receptor.

One aspect of the invention relates to a compound having the general structure shown in Formula I:

10



or a pharmaceutically acceptable salt or solvate thereof; wherein:

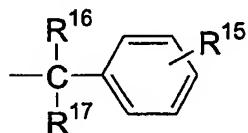
15 R¹ is

R² is selected from the group consisting of H, alkyl, aryl, arylalkyl, heteroarylalkyl, alkylketone, arylketone, alkyl, haloalkyl, cycloalkyl, cycloheteroalkyl, cycloalkylalkyl, alkylsulfonyl, arylsulfonyl, alkoxyalkyl, or amide;

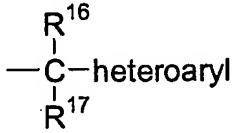
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R^3 is selected from the group consisting of aryl, 6-membered heteroaryl, fluorenyl; and diphenylmethyl, 6 membered heteroaryl-N-oxide,



and



, wherein said aryl, fluorenyl,

- 5 diphenyl or heteroaryl is optionally substituted with 1-4 substituents which can be the same or different and are independently selected from the group consisting of R^{11} , R^{12} , R^{13} , R^{14} and R^{15} ;

R^4 is 1-3 substituents selected from the group consisting of H, halo, alkyl, haloalkyl, alkoxy, cycloalkyl, cycloheteroalkyl, amide, CF_3 , OCF_3 , aryl, heteroaryl, $-XR^7$, $-C(O)C_3-C_8$ cycloalkyl, $-C(O)C_3-C_8$ cycloheteroalkyl, $-(C_1-C_6)$ alkyl- $N(R^{21})SO_2R^{22}$, $-(C_1-C_6)$ alkyl- $C(O)NR^{20}R^{21}$, -CN, $-CO_2H$, $-CO_2R^{22}$, R^8 -aryl(C_1-C_6)alkyl-, R^8 -heteroaryl(C_1-C_6)alkyl-, $-C(O)-(C_1-C_6)$ alkyl, R^8 -aryl- $C(O)-$, $-C(O)NR^{21}R^{22}$, $-C(O)NH_2$, $-C(O)N(H)OH$, $-(C_1-C_6)$ alkyl- $N(R^{21})C(O)R^{22}$, $-(C_1-C_6)$ alkyl- $N(R^{21})CO_2R^{22}$, $-(C_1-C_6)$ alkyl- $N(R^{21})C(O)NR^{21}R^{22}$, $-(C_1-C_6)$ alkyl- $NR^{21}R^{22}$, $-(C_1-C_6)$ alkyl- NH_2 , (C_1-C_6) alkyl- $SO_2NR^{21}R^{22}$ and $-SO_2NR^{21}R^{22}$, wherein R^4 can be the same or different and is independently selected when there is more than one R^4 present;

R^5 is selected from the group consisting of H, arylalkyl, (C_1-C_6)alkyl, R^8 -aryl(C_1-C_6)alkyl-, R^8 -heteroaryl(C_1-C_6)alkyl-, $-SO_2-(C_1-C_6)$ alkyl, $-SO_2-(C_3-C_6)$ cycloalkyl, $-SO_2$ -aryl, R^8 -aryl- SO_2- , $-C(O)-(C_1-C_6)$ alkyl, $-C(O)-(C_4-C_6)$ cycloalkyl, R^8 -aryl- $C(O)-$, $-C(O)NR^{21}R^{22}$, and $-SO_2NR^{21}R^{22}$;

R^6 is H, $-(C_1-C_6)$ alkyl, or $-(C_1-C_6)$ haloalkyl;

R^7 is selected from the group consisting of aryl, substituted aryl, heteroaryl, alkyl, haloalkyl and cycloalkyl;

25 R^8 is 1, 2 or 3 substituents selected from the group consisting of H, halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, $-CF_3$, $-OCF_3$, $CH_3C(O)-$, -CN, CH_3SO_2- , CF_3SO_2- and $-NH_2$, wherein R^8 can be the same or different and is independently selected when there are more than one R^8 present;

R^9 , R^{10} and B can be the same or different and are each
30 independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, and $-(C_1-C_6)$ haloalkyl;

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R¹¹ and R¹² can be the same or different and are each independently selected from the group consisting of (C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, halogen, -NR¹⁹R²⁰, -OH, CF₃, -OCH₃, -O-acyl, and -OCF₃;

R¹³ is selected from the group consisting of hydrogen, R¹¹, H,
5 phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR₁₉, pyridyl-N-oxide, pyrimidinyl, pyrazinyl, N(R₂₀)CONR₂₀R₂₁, -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH((C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHCOCF₃, -NSO₂N((C₁-C₆)alkyl)₂, -NSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, (C₃-C₁₀)cycloalkyl, -SR²², -SOR²², -SO₂R²², -
10 SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CONR¹⁹R²⁰, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R₁₉, -Si(CH₃)₃ and -B(OC(CH₃)₂)₂;

R¹⁴ is selected from the group consisting of (C₁-C₆)alkyl, -(C₁-C₆)haloalkyl -NH₂ and R¹⁵-phenyl;

15 R¹⁵ is 1-3 substituents selected from the group consisting of hydrogen, (C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, -CF₃, -CO₂R²⁰, -CN, (C₁-C₆)alkoxy and halogen; wherein R¹⁵ can be the same or different and is independently selected when there are more than one R¹⁵ present;

20 R¹⁶ and R¹⁷ can each be the same or different and are each independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl, or

R¹⁶ and R¹⁷ together are a C₂-C₅ alkylene group and with the carbon to which they are attached from a spiro ring of 3 to 6 carbon atoms;

25 R¹⁹, R²⁰ and R²¹ can each be the same or different and are each independently selected from the group consisting of H, (C₁-C₆)alkyl and (C₃-C₆)cycloalkyl;

R²² is selected from the group consisting of (C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, (C₂-C₆)hydroxyalkyl, (C₂-C₆)alkylene, (C₃-C₆)cycloalkyl, aryl and aryl(C₁-C₆)alkyl-;

30 A is selected from the group consisting of H, (C₁-C₆)alkyl, and (C₂-C₆) alkenyl.

M is aryl or heteroaryl optionally substituted with R⁴;

Q is CH or N; and

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X is selected from the group consisting of CH₂, SO₂, SO, S, and O, with the following proviso:

when R¹ is phenyl, pyridyl, thiophenyl or naphthyl, R² cannot be H, -(C₁-C₆)alkyl or -C(O)-(C₁-C₆)alkyl.

5

Another aspect of the invention relates to a pharmaceutical composition for treatment of HIV comprising one or more compounds of formula I.

Yet another aspect of the invention relates to a method of treating
10 Human Immunodeficiency Virus comprising administering to a patient in need of such treatment a therapeutically effective amount of one or more compounds of formula I. A further aspect of the invention relates to a method of treating solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic
15 dermatitis, psoriasis, asthma, allergies or multiple sclerosis comprising administering to a patient in need of such treatment a therapeutically effective amount of one or more compounds of formula I.

Still another aspect of this invention relates to a method of treating
Human Immuno-deficiency Virus comprising administering to a patient in
20 need of such treatment the one or more compounds of formula I in combination with one or more antiviral or other agents useful in the treatment. A further aspect of this invention relates to a method of treating solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma
25 or allergies comprising administering to a patient in need of such treatment one or more compounds of formula I in combination with one or more antiviral or other agents useful in the treatment.

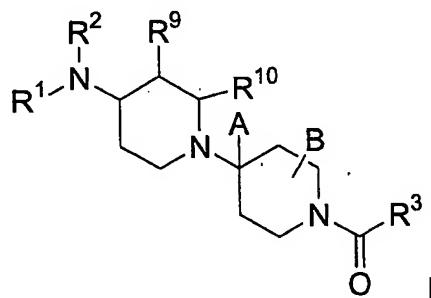
The CCR5 and antiviral or other agents which are components of the combination can be administered in a single dosage or administered
30 separately. A kit comprising separate dosage forms of the actives is also contemplated.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a compound having the general structure shown in Formula I:

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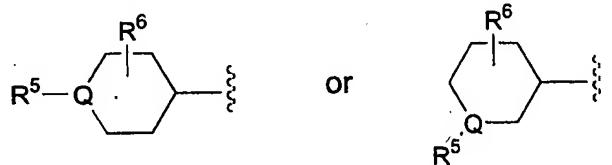


or a pharmaceutically acceptable salt or solvate thereof; wherein:

10

wherein R¹, R², R³, R⁹, R¹⁰, A and B are defined as above.

When R₁ is



15 Q is preferably CH or N, and R² is preferably alkyl, aryl or benzyl.

When R₁ is M-R⁴, R₂ is preferably benzyl, phenyl or

cyclopropylmethyl.

As used herein, the following terms are used as defined below
20 unless otherwise indicated.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain 1 to about 6 carbon atoms in the chain. Branched alkyl means that one or more lower alkyl groups such as

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methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. Preferred alkyl groups in the present invention are lower alkyl groups. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl, decyl, trifluoromethyl and cyclopropylmethyl.

5 "Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

10 "Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

15 "Haloalkyl" or "halogenated alkyl" means alkyl having one or more halo atom substituents. Preferably, the haloalkyl is a haloalkyl. Non-limiting examples include -CH₂Cl, -CHCl₂, -CCl₃, -CH₂F, -CHF₂, -CF₃, -CH₂-CH₂F, -CH₂CHF₂, -CH₂CF₃ and -CF₂CF₃.

20 "Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of aryl, heteroaryl, aralkyl, alkylamino, arylamino, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, aralkyloxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl, Y₁Y₂N-, Y₁Y₂N-alkyl-, Y₁Y₂NC(O)- and Y₁Y₂NSO₂-, wherein Y₁ and Y₂ may be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl.

30 "Cycloalkyl" means a non-aromatic mono- or multicyclic fused ring system comprising 3 to 10 ring carbon atoms, preferably 3 to 7 ring carbon atoms, more preferably 3 to 6 ring carbon atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which

may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornenyl, adamantyl and the like.

5

"Cycloheteroalkyl" means a non-aromatic mono- or multicyclic fused ring system comprising 3 to 10 ring carbon atoms, preferably 3 to 7 ring carbon atoms, more preferably 3 to 6 ring carbon atoms, wherein the cycloheteroaryl has 1 or 2 heteroatoms independently selected from O, S or 10 N, said heteroatom(s) interrupting a carbocyclic ring structure provided that the rings do not contain adjacent oxygen and/or sulfur atoms. The cycloheteroalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above.

15

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising 6 to 14 ring carbon atoms, preferably 6 to 10 ring carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and 20 naphthyl.

25

"Heteroaryl" represents cyclic aromatic groups of 5 or 6 ring atoms or bicyclic groups of 11 to 12 ring atoms having 1 or 2 heteroatoms independently selected from O, S or N, said heteroatom(s) interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, provided that the rings do not contain adjacent oxygen and/or sulfur atoms. Preferred heteroaryls contain 5 to 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. Nitrogen atoms can form an N-oxide. All regioisomers are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl. Useful 6-membered heteroaryl groups include pyridyl, pyrimidinyl,

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pyrazinyl, pyridazinyl and the like and the N-oxides thereof. Useful 5-membered heteroaryl rings include furyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, isoxazolyl and the like. Useful bicyclic groups include benzo-fused ring systems derived from the heteroaryl groups named above, e.g. quinolyl, phthalazinyl, quinazolinyl, benzofuranyl, benzothienyl, indolyl and the like.

Amide is represented by RCONH₂ wherein one or both of the hydrogen atoms in RCONH₂ can be substituted by an alkyl group and alkyl has the same meaning as defined above.

10 Arylalkyl or aralkyl represents a moiety containing an aryl group linked to the main group or ring via an alkyl.

Alkylketone represents a moiety containing an alkyl group linked to the main group or ring via a ketone.

15 Arylketone represents a moiety containing an aryl group linked to the main group or ring via a ketone.

Alkylaryl represents a moiety containing an alkyl linked to the main group or ring via an aryl group.

Heteroarylalkyl represents a moiety containing a heteroaryl group linked to the main group or ring via an alkyl.

20 The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "solvate" as used herein means an aggregate that consists of a solute ion or molecule with one or more solvent molecules, for example, a hydrate containing such ions.

25 As used herein, the terms "composition" and "formulation" are intended to encompass a product comprising the specified ingredients, as well as any product which results, directly or indirectly, from combination of the specified ingredients.

"Patient" includes mammals and other animals.

30 "Mammal" includes humans and other mammalian animals.

The term "therapeutically effective amount" is intended to mean an amount of a therapeutic agent of the compound of formula I that will have an effect on a tissue, system, animal or patient that is being sought by the

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administrator (such as a researcher, doctor or veterinarian), which includes alleviation of the symptoms of the condition or disease being treated and the prevention, slowing or halting of progression of the disease or condition, for example, the inflammatory, immunomodulatory or respiratory diseases discussed herein.

5 Prodrugs and solvates of the compounds of the invention are also contemplated within the scope of this invention. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or 10 chemical processes to yield a compound of formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volume 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and 15 Pergamon Press, both of which are incorporated herein by reference thereto.

The compounds of formula I can form salts, solvates and prodrugs which are also within the scope of this invention. Reference to a compound of formula I herein is understood to include reference to salts, solvates and prodrugs thereof, unless otherwise indicated.

20 The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of formula I contains both a basic moiety, such as, but not limited to, a pyridine or 25 imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the formula I may be formed, for 30 example, by reacting a compound of formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

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Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, 5 fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, 10 propionates, salicylates, succinates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) undecanoates, and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by 15 S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; and Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydрабamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts 20 with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, 25 bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all

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acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of formula I, and salts and solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or 5 imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates 10 of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the 15 invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to 20 equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

The term "nucleoside and nucleotide reverse transcriptase inhibitors" ("NRTI" s) as used herein means nucleosides and nucleotides and 25 analogues thereof that inhibit the activity of HIV-1 reverse transcriptase, the enzyme which catalyzes the conversion of viral genomic HIV-1 RNA into proviral HIV-1 DNA.

Typical suitable NRTIs include zidovudine (AZT) available under the RETROVIR tradename from Glaxo-Wellcome Inc., Research Triangle, NC 30 27709; didanosine (ddI) available under the VIDEX tradename from Bristol-Myers Squibb Co., Princeton, NJ 08543; zalcitabine (ddC) available under the HVID tradename from Roche Pharmaceuticals, Nutley, NJ 07110; stavudine (d4T) available under the ZERIT trademark from Bristol-Myers

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Squibb Co., Princeton, NJ 08543; lamivudine (3TC) available under the EPIVIR trademark from Glaxo-Wellcome Research Triangle, NC 27709; abacavir (1592U89) disclosed in WO96/30025 and available under the ZIAGEN trademark from Glaxo-Wellcome Research Triangle, NC 27709;

5 adefovir dipivoxil [bis(POM)-PMEA] available under the PREVON trademark from Gilead Sciences, Foster City, CA 94404; lobucavir (BMS-180194), a nucleoside reverse transcriptase inhibitor disclosed in EP-0358154 and EP-0736533 and under development by Bristol-Myers Squibb, Princeton, NJ 08543; BCH-10652, a reverse transcriptase inhibitor

10 (in the form of a racemic mixture of BCH-10618 and BCH-10619) under development by Biochem Pharma, Laval, Quebec H7V, 4A7, Canada; emtricitabine [(-)-FTC] licensed from Emory University under Emory Univ. U.S. Patent No. 5,814,639 and under development by Triangle Pharmaceuticals, Durham, NC 27707; beta-L-FD4 (also called beta-L-D4C and named beta-L-2', 3'-dideoxy-5-fluoro-cytidine) licensed by Yale University to Vion Pharmaceuticals, New Haven CT 06511; DAPD, the purine nucleoside, (-)-beta-D-2,6,-diamino-purine dioxolane disclosed in EP 0656778 and licensed by Emory University and the University of Georgia to Triangle Pharmaceuticals, Durham, NC 27707; and Idenosine (FddA), 9-

15 (2,3-dideoxy-2-fluoro-b-D-threo-pentofuranosyl)adenine, an acid stable purine-based reverse transcriptase inhibitor discovered by the NIH and under development by U.S. Bioscience Inc., West Conshohoken, PA 19428.

The term "non-nucleoside reverse transcriptase inhibitors" ("NNRTI"s) as used herein means non-nucleosides that inhibit the activity of HIV-1 reverse transcriptase.

Typical suitable NNRTIs include nevirapine (BI-RG-587) available under the VIRAMUNE trademark from Boehringer Ingelheim, the manufacturer for Roxane Laboratories, Columbus, OH 43216; delavirdine (BHAP, U-90152) available under the REScriptor trademark from Pharmacia & Upjohn Co., Bridgewater NJ 08807; efavirenz (DMP-266) a benzoxazin-2-one disclosed in WO94/03440 and available under the SUSTIVA trademark from DuPont Pharmaceutical Co., Wilmington, DE

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19880-0723; PNU-142721, a fuopyridine-thio-pyrimide under development by Pharmacia and Upjohn, Bridgewater NJ 08807; AG-1549 (formerly Shionogi # S-1153); 5-(3,5-dichlorophenyl)- thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbonate disclosed in WO 96 /10019 and under clinical development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; MKC-442 (1-(ethoxy-methyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione) discovered by Mitsubishi Chemical Co. and under development by Triangle Pharmaceuticals, Durham, NC 27707; and (+)-calanolide A (NSC-675451) and B, coumarin derivatives disclosed in NIH U.S. Patent No. 5,489,697, licensed to Med Chem Research, which is co-developing (+) calanolide A with Vita-Invest as an orally administrable product.

The term "protease inhibitor" ("PI") as used herein means inhibitors of the HIV-1 protease, an enzyme required for the proteolytic cleavage of viral polyprotein precursors (e.g., viral GAG and GAG Pol polyproteins), into the individual functional proteins found in infectious HIV-1. HIV protease inhibitors include compounds having a peptidomimetic structure, high molecular weight (7600 daltons) and substantial peptide character, e.g. CRIXIVAN(available from Merck) as well as nonpeptide protease inhibitors e.g., VIRACEPT (available from Agouron).

Typical suitable PIs include saquinavir (Ro 31-8959) available in hard gel capsules under the INVIRASE tradename and as soft gel capsules under the FORTOVASE tradename from Roche Pharmaceuticals, Nutley, NJ 07110-1199; ritonavir (ABT-538) available under the NORVIR tradename from Abbott Laboratories, Abbott Park, IL 60064; indinavir (MK-639) available under the CRIXIVAN tradename from Merck & Co., Inc., West Point, PA 19486-0004; nelfnavir (AG-1343) available under the VIRACEPT tradename from Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; amprenavir (141W94), tradename AGENERASE, a non-peptide protease inhibitor under development by Vertex Pharmaceuticals, Inc., Cambridge, MA 02139-4211 and available from Glaxo-Wellcome, Research Triangle, NC under an expanded access program; lasinavir (BMS-234475) available from Bristol-Myers Squibb, Princeton, NJ 08543

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(originally discovered by Novartis, Basel, Switzerland (CGP-61755); DMP-450, a cyclic urea discovered by Dupont and under development by Triangle Pharmaceuticals; BMS-2322623, an azapeptide under development by Bristol-Myers Squibb, Princeton, NJ 08543, as a 2nd-generation HIV-1 PI; ABT-378 under development by Abbott , Abbott Park, IL 60064; and AG-1549 an orally active imidazole carbamate discovered by Shionogi (Shionogi #S-1153) and under development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020.

Other antiviral agents include hydroxyurea, ribavirin, IL-2, IL-12, 10 pentafuside and Yissum Project No. 11607. Hydroxyurea (Droxia), a ribonucleoside triphosphate reductase inhibitor, the enzyme involved in the activation of T-cells, was discovered at the NCI and is under development by Bristol-Myers Squibb; in preclinical studies, it was shown to have a synergistic effect on the activity of didanosine and has been studied with 15 stavudine. IL-2 is disclosed in Ajinomoto EP-0142268 , Takeda EP-0176299, and Chiron U. S. Patent Nos. RE 33653, 4530787, 4569790, 4604377, 4748234, 4752585, and 4949314, and is available under the PROLEUKIN (aldesleukin) tradename from Chiron Corp., Emeryville, CA 94608-2997 as a lyophilized powder for IV infusion or sc administration 20 upon reconstitution and dilution with water; a dose of about 1 to about 20 million IU/day, sc is preferred; a dose of about 15 million IU/day, sc is more preferred. IL-12 is disclosed in WO96/25171 and is available from Roche Pharmaceuticals, Nutley, NJ 07110-1199 and American Home Products, Madison, NJ 07940; a dose of about 0.5 microgram/kg/day to about 10 25 microgram/kg/day, sc is preferred. Pentafuside (DP-178, T-20) a 36-amino acid synthetic peptide, disclosed in U.S. Patent No.5,464,933 licensed from Duke University to Trimeris which is developing pentafuside in collaboration with Duke University; pentafuside acts by inhibiting fusion of HIV-1 to target membranes. Pentafuside (3-100 mg /day) is given as a continuous sc 30 infusion or injection together with efavirenz and 2 PI's to HIV-1 positive patients refractory to a triple combination therapy; use of 100 mg/day is preferred. Yissum Project No. 11607, a synthetic protein based on the HIV -1 Vif protein, is under preclinical development by Yissum Research

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Development Co., Jerusalem 91042 , Israel. Ribavirin, 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, is available from ICN Pharmaceuticals, Inc., Costa Mesa, CA; its manufacture and formulation are described in U.S. Patent No. 4,211,771.

5 The term "anti-HIV-1 therapy" as used herein means any anti-HIV-1 drug found useful for treating HIV-1 infections in man alone, or as part of multidrug combination therapies, especially the HAART triple and quadruple combination therapies. Typical suitable known anti-HIV-1 therapies include, but are not limited to multidrug combination therapies
10 such as (i) at least three anti-HIV-1 drugs selected from two NRTIs, one PI, a second PI, and one NNRTI; and (ii) at least two anti-HIV-1 drugs selected from NNRTIs and PIs. Typical suitable HAART - multidrug combination therapies include:

15 (a) triple combination therapies such as two NRTIs and one PI ; or
 (b) two NRTIs and one NNRTI ; and (c) quadruple combination therapies such as two NRTIs , one PI and a second PI or one NNRTI. In treatment of naive patients, it is preferred to start anti-HIV-1 treatment with the triple combination therapy; the use of two NRTIs and one PI is prefered unless there is intolerance to PIs. Drug compliance is essential. The CD4⁺ and
20 HIV-1-RNA plasma levels should be monitored every 3-6 months. Should viral load plateau, a fourth drug,e.g., one PI or one NNRTI could be added.
See the table below wherein typical therapies are further described:

ANTI-HIV-1 MULTI DRUG COMBINATION THERAPIES

25 A. Triple Combination Therapies

1. Two NRTIs¹ + one PI²
2. Two NRTIs¹ + one NNRTI³

30 B. Quadruple Combination Therapies⁴

- Two NRTIs + one PI + a second PI or one NNRTI

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C. ALTERNATIVES:⁵

Two NRTI¹

One NRTI⁵ + one PI²

Two PIs⁶ + one NRTI⁷ or NNRTI³

5 One PI² + one NRTI⁷ + one NNRTI³

FOOTNOTES TO TABLE

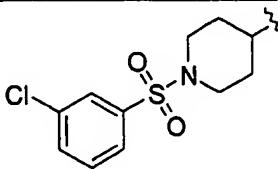
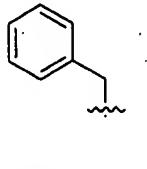
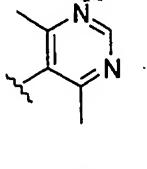
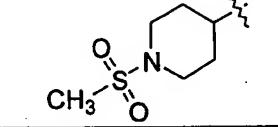
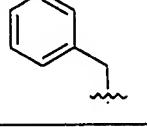
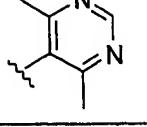
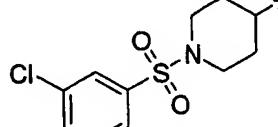
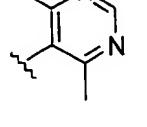
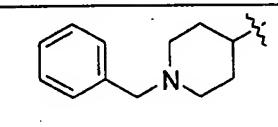
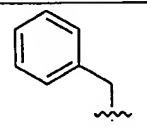
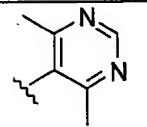
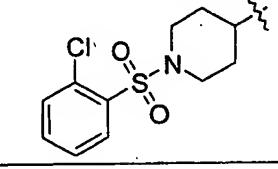
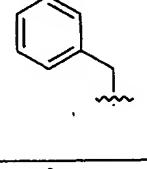
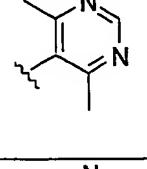
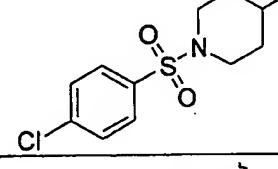
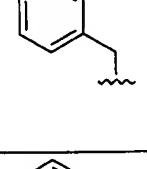
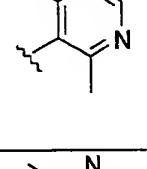
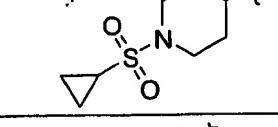
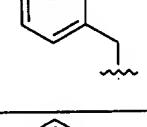
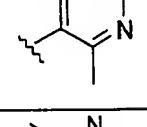
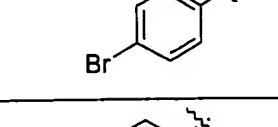
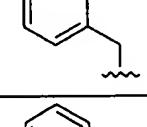
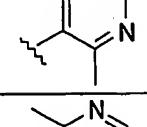
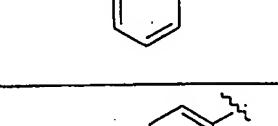
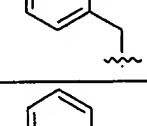
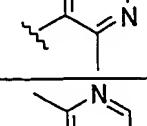
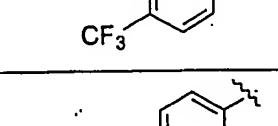
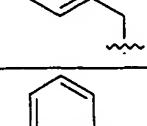
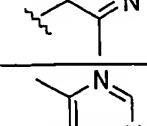
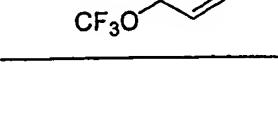
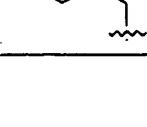
1. One of the following: zidovudine + lamivudine; zidovudine + didanosine; stavudine + lamivudine; stavudine + didanosine; zidovudine + zalcitabine
- 10 2. Indinavir, nelfinavir, ritonavir or saquinavir soft gel capsules.
3. Nevirapine or delavirdine.
4. See A-M. Vandamne et al Antiviral Chemistry & Chemotherapy 9:187 at p. 193-197 and Figures 1 + 2.
- 15 5. Alternative regimens are for patients unable to take a recommended regimen because of compliance problems or toxicity, and for those who fail or relapse on a recommended regimen. Double nucleoside combinations may lead to HIV-resistance and clinical failure in many patients.
- 20 6. Most data obtained with saquinavir and ritonavir (each 400 mg bid).
7. Zidovudine, stavudine or didanosine.

Specific examples of compounds of the present invention include,
25 but are not limited to, compounds wherein R¹, R² and R³ are as defined in the following table:

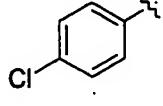
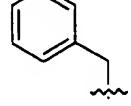
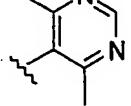
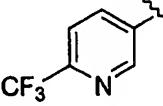
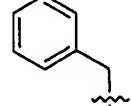
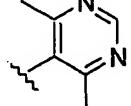
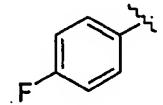
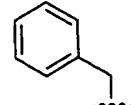
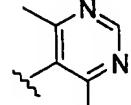
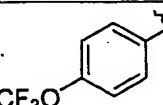
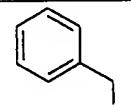
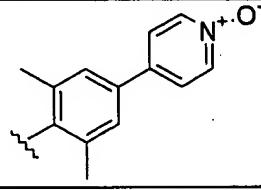
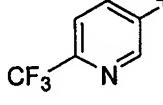
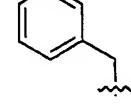
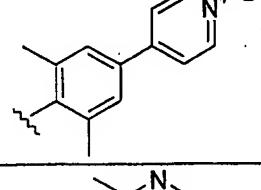
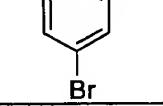
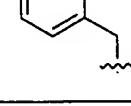
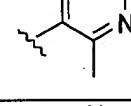
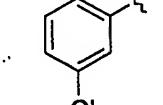
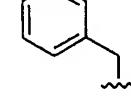
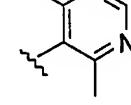
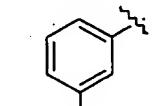
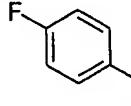
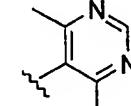
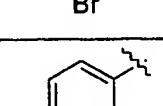
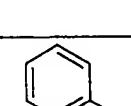
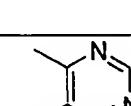
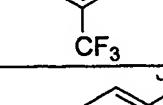
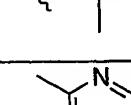
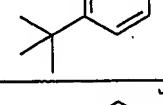
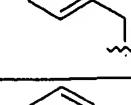
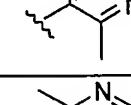
TABLE 1

#	R ¹	R ²	R ³
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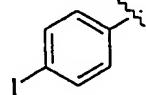
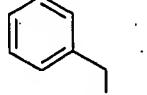
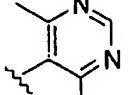
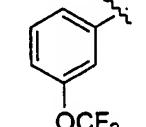
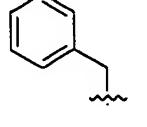
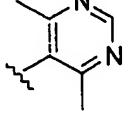
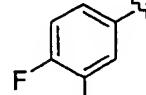
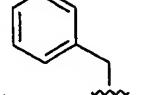
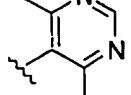
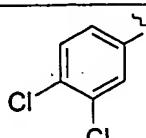
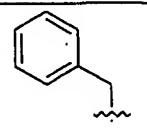
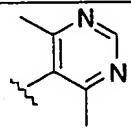
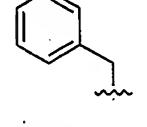
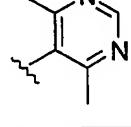
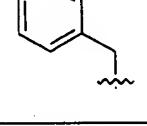
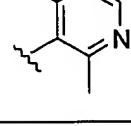
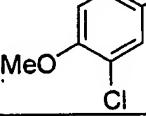
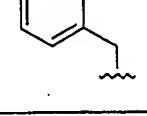
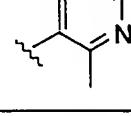
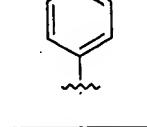
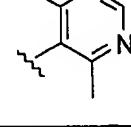
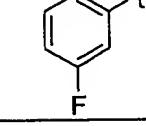
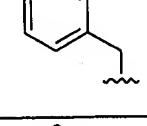
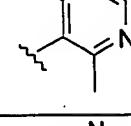
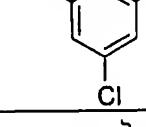
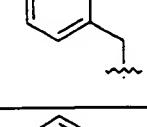
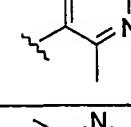
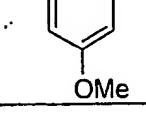
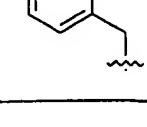
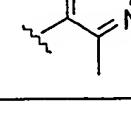
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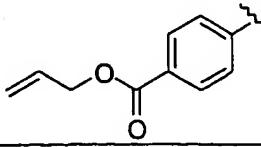
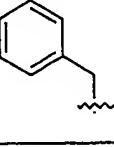
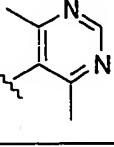
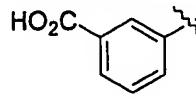
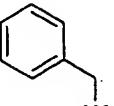
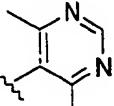
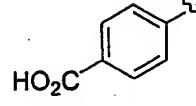
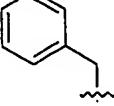
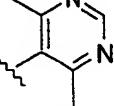
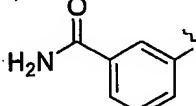
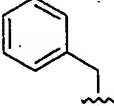
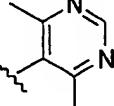
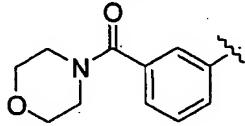
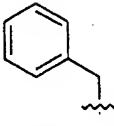
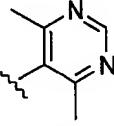
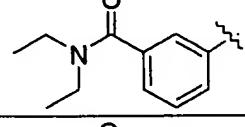
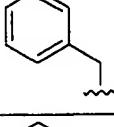
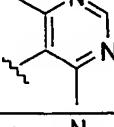
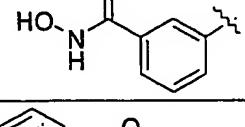
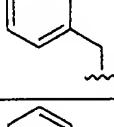
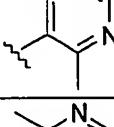
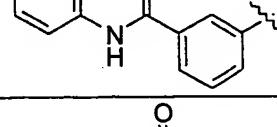
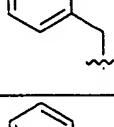
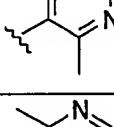
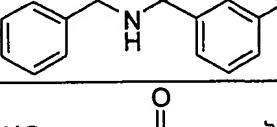
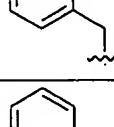
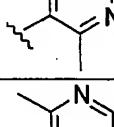
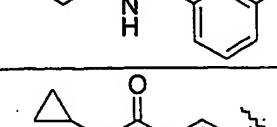
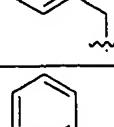
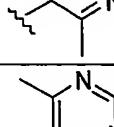
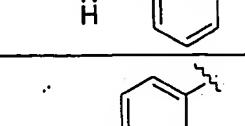
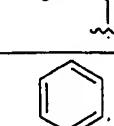
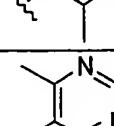
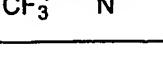
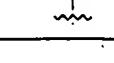
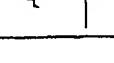
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35	<chem>*c1ccc(Cl)c(C(F)(F)F)cc1</chem>	<chem>*c1ccccc1Cc2ccncc2</chem>	<chem>*c1ccncc2c(C)c(C)c(*)nc12</chem>
36	<chem>*c1ccc(F)c(F)cc1</chem>	<chem>*c1ccccc1Cc2ccncc2</chem>	<chem>*c1ccncc2c(C)c(C)c(*)nc12</chem>
37	<chem>*c1ccc(*)cc1</chem>	<chem>*c1ccccc1Cc2ccncc2</chem>	<chem>*c1ccncc2c(C)c(C)c(*)nc12</chem>
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41	<chem>*c1ccccc1Cc2ccncc2</chem>	<chem>*c1ccccc1Cc2ccncc2</chem>	<chem>*c1ccncc2c(C)c(C)c(*)nc12</chem>
42	<chem>*c1ccc(F)cc1</chem>	<chem>*c1ccccc1Cc2ccncc2</chem>	<chem>*c1ccncc2c(C)c(C)c(*)nc12</chem>
43	<chem>*c1ccc(*)cc1</chem>	<chem>*c1ccccc1Cc2ccncc2</chem>	<chem>*c1ccncc2c(C)c(C)c(*)nc12</chem>
44	<chem>*c1ccccc1Cc2ccncc2</chem>	<chem>*c1ccccc1Cc2ccncc2</chem>	<chem>*c1ccncc2c(C)c(C)c(*)nc12</chem>
45	<chem>*c1ccc2c(c1)N3CCOCC3</chem>	<chem>*c1ccccc1Cc2ccncc2</chem>	<chem>*c1ccncc2c(C)c(C)c(*)nc12</chem>

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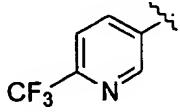
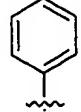
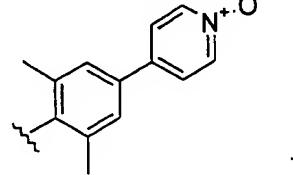
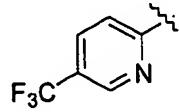
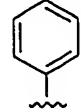
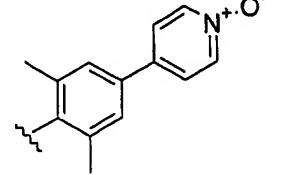
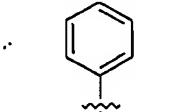
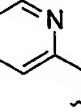
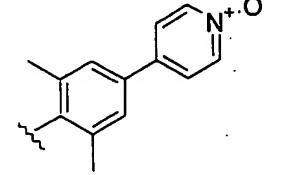
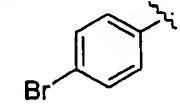
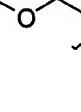
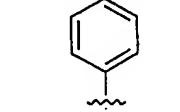
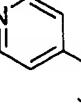
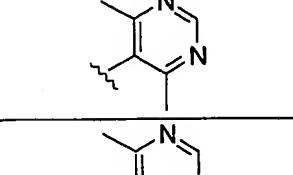
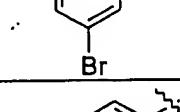
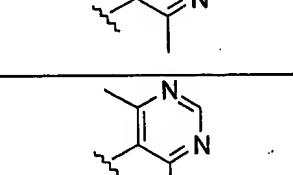
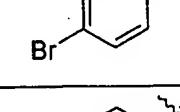
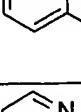
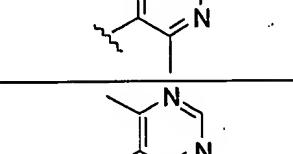
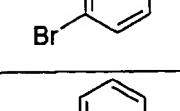
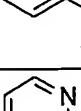
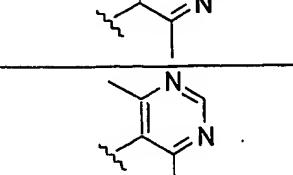
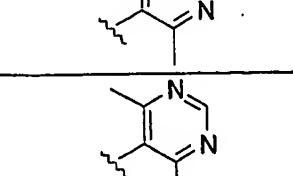
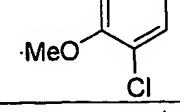
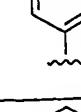
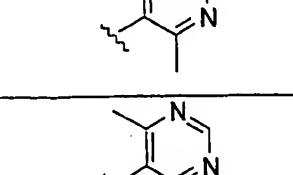
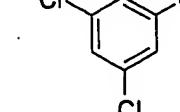
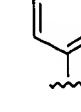
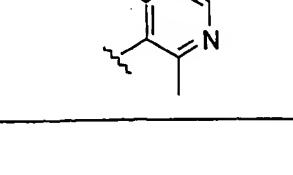
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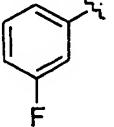
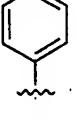
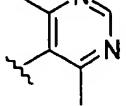
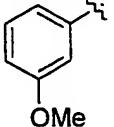
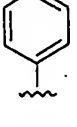
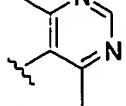
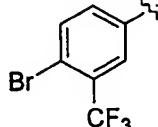
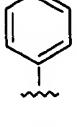
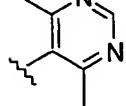
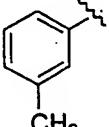
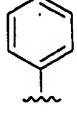
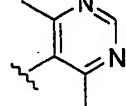
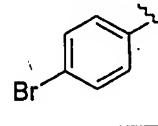
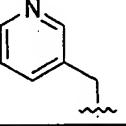
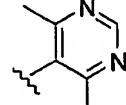
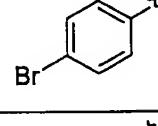
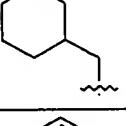
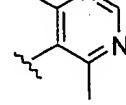
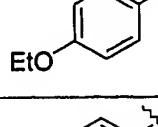
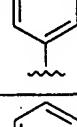
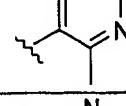
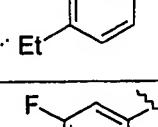
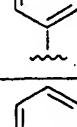
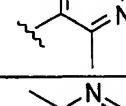
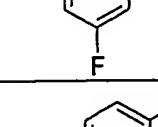
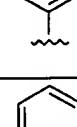
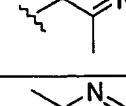
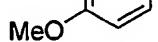
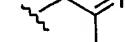
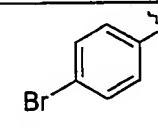
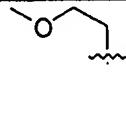
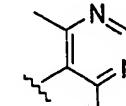
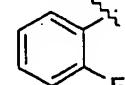
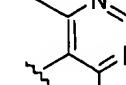
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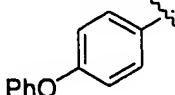
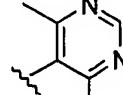
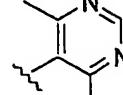
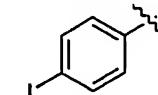
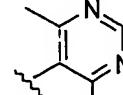
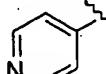
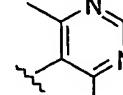
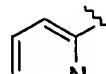
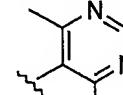
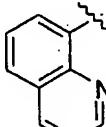
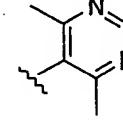
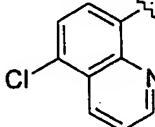
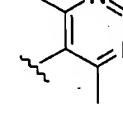
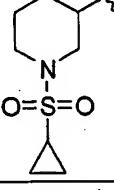
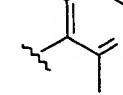
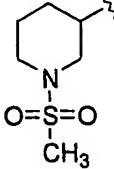
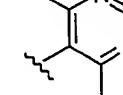
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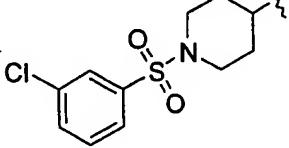
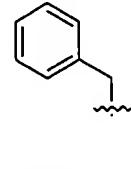
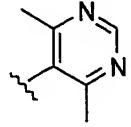
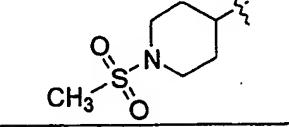
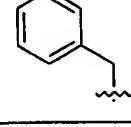
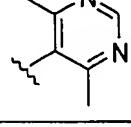
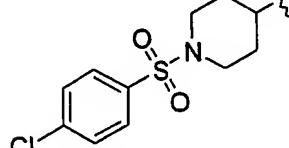
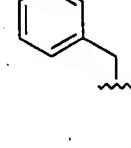
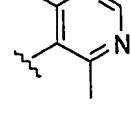
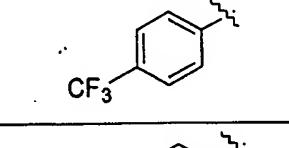
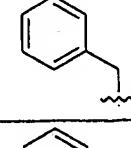
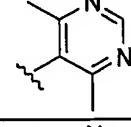
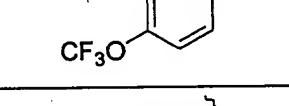
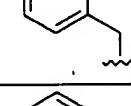
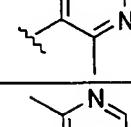
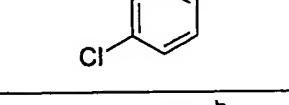
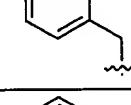
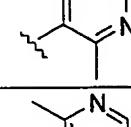
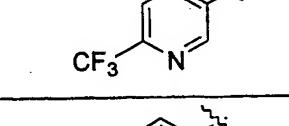
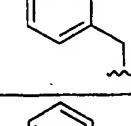
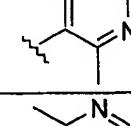
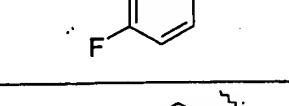
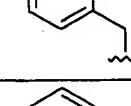
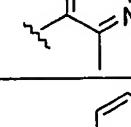
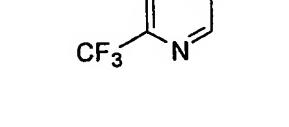
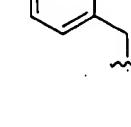
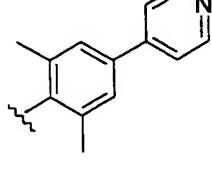
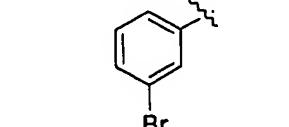
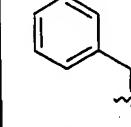
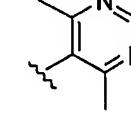
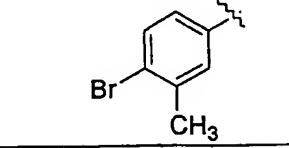
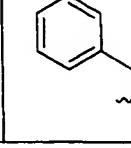
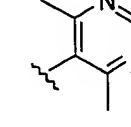
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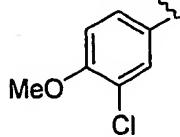
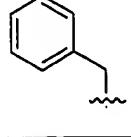
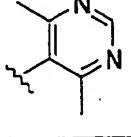
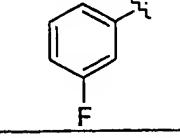
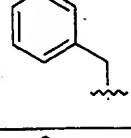
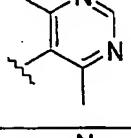
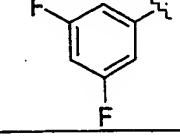
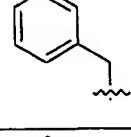
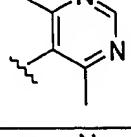
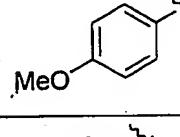
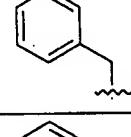
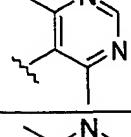
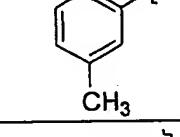
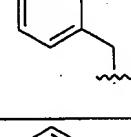
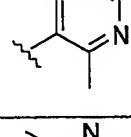
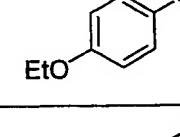
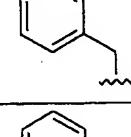
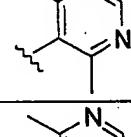
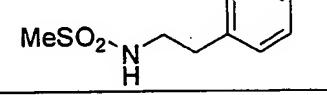
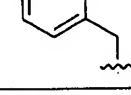
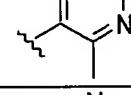
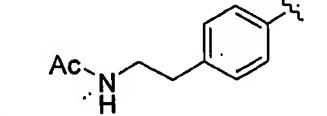
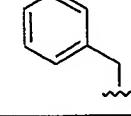
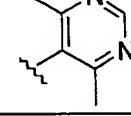
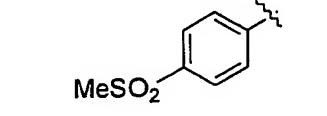
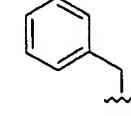
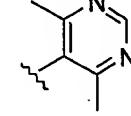
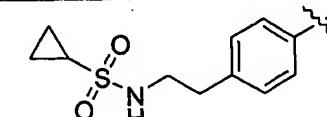
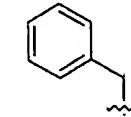
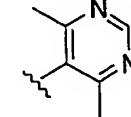
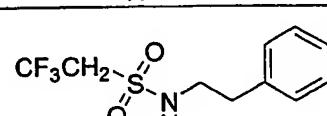
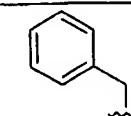
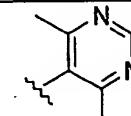
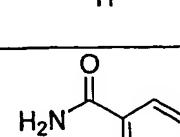
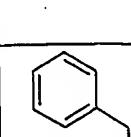
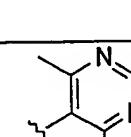
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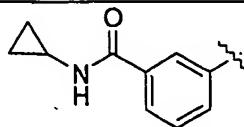
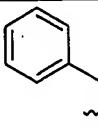
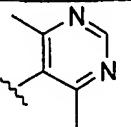
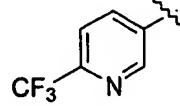
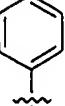
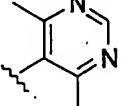
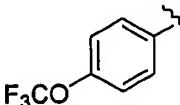
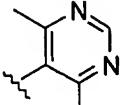
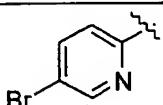
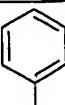
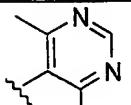
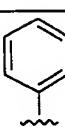
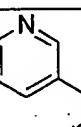
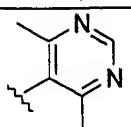
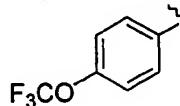
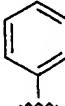
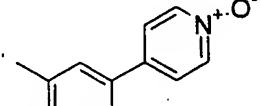
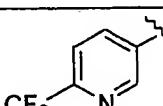
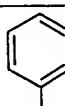
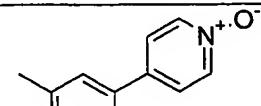
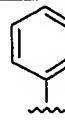
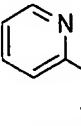
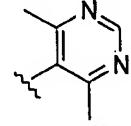
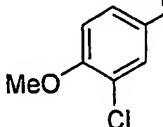
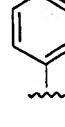
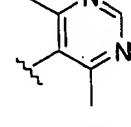
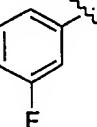
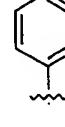
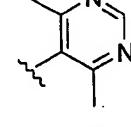
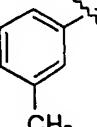
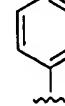
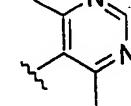
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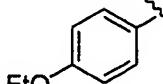
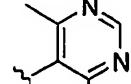
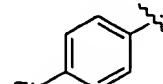
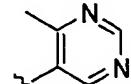
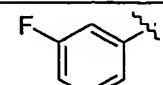
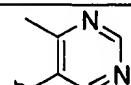
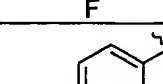
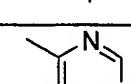
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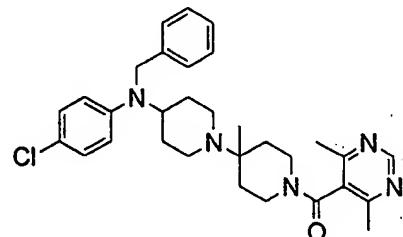
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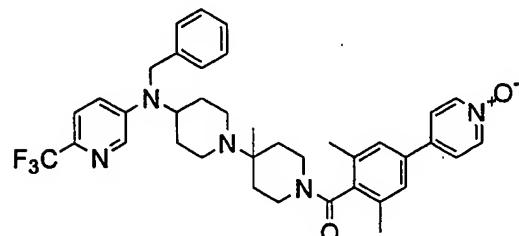
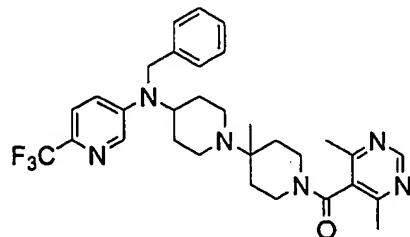
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Even more preferably, the compounds of the present invention are represented by the following formulae:

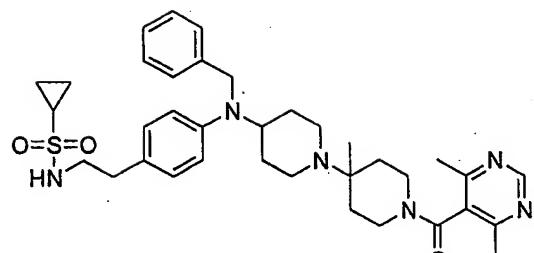
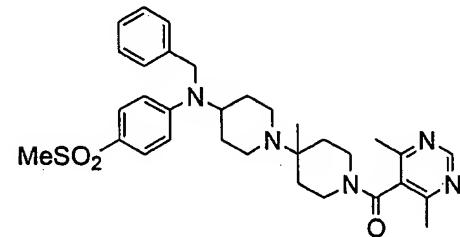
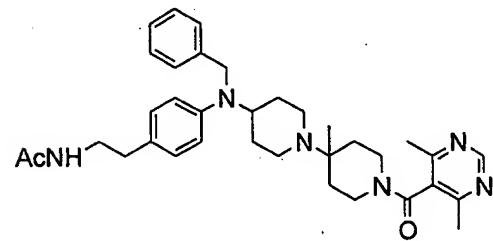
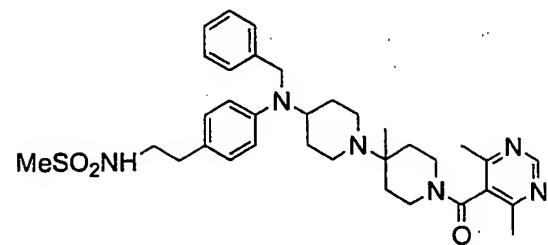


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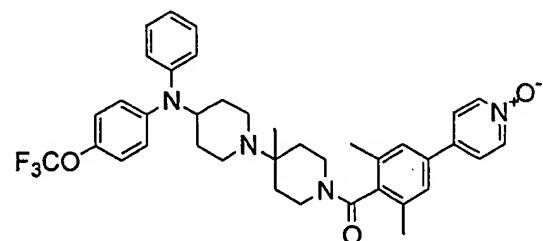
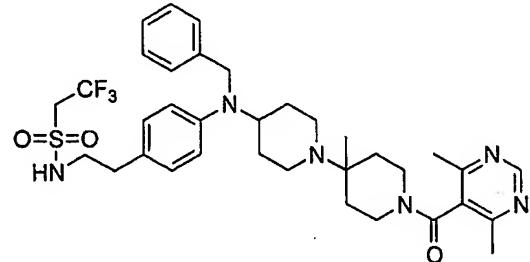


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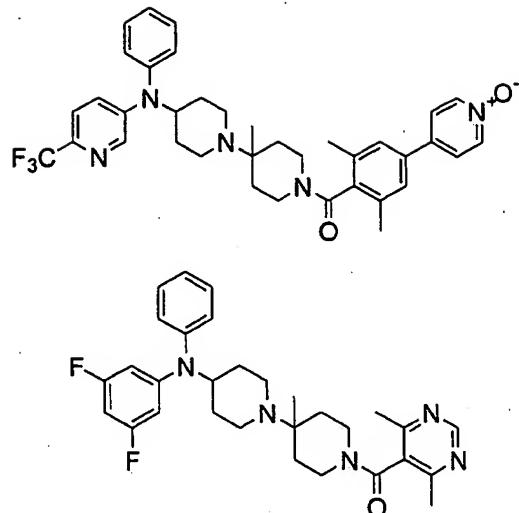
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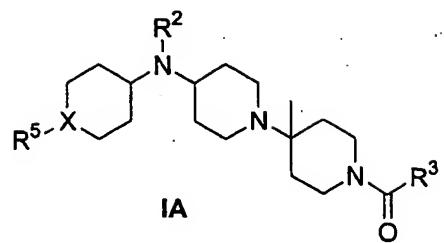


The compound of the present invention, also referred to herein as the inventive compound, is particularly useful as a CCR5 antagonist.

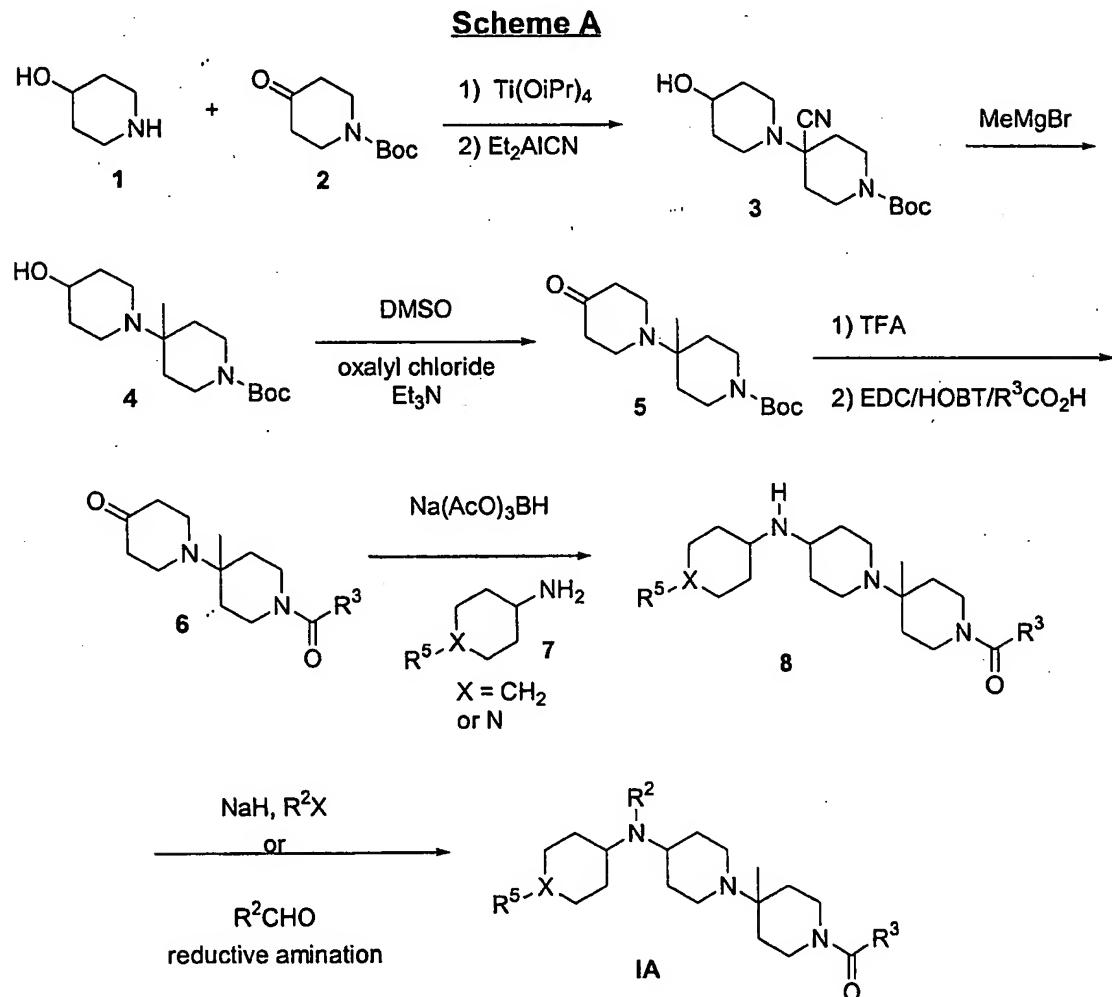
Compounds of the invention can be made by the procedures known in the art, for example by the procedures described in the following reaction schemes, by the methods described in the examples below, and by using the methods described in US patents 5,883,096; 6,037,352; 5,889,006; 5,952,349; and 5,977,138.

The following solvents and reagents may be referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxy-benzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et₃N); diethyl ether (Et₂O); tert-butoxycarbonyl (BOC); 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); dimethylsulfoxide (DMSO); p-toluene sulfonic acid (p-TSA); potassium bis(trimethylsilyl)-amide (KHMDA); 4-dimethylaminopyridine (DMAP); N,N,N-diisopropylethylamine (DIPEA); and 1-(3-dimethyl-aminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI). RT is room temperature.

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Compounds of formula **IA** wherein X is CH₂ or N, R² is alkyl, aryl, or benzyl, and R³ and R⁵ is as defined in the summary of the invention are prepared according to **Scheme A**.

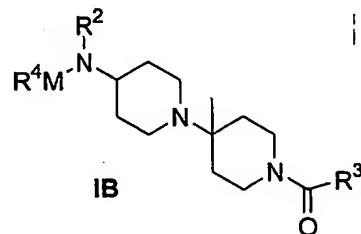


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For the synthesis of compounds of formula **IA**, 4-hydroxypiperidine **1** and N-Boc-4-piperidone **2** are sequentially treated with titanium

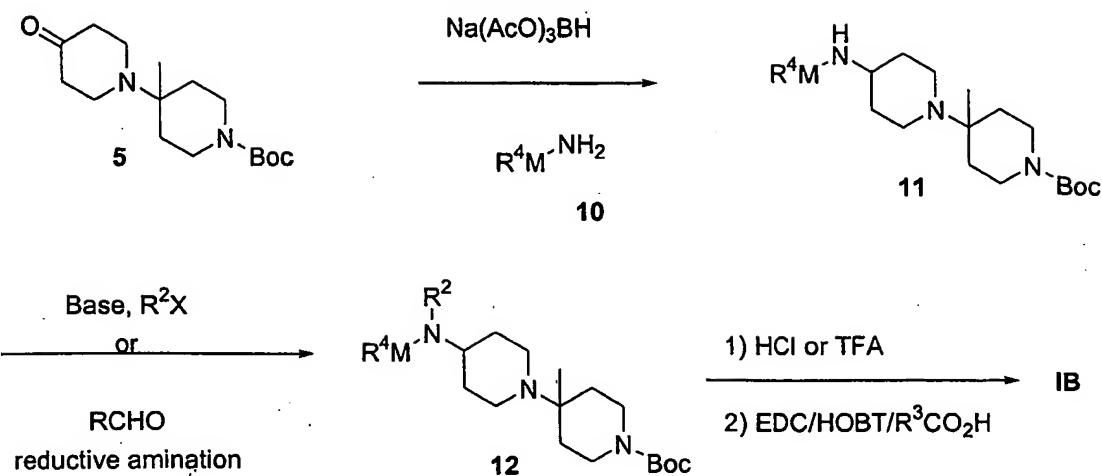
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isopropoxide and diethyl aluminum cyanide to furnish the cyano-amine 3. The cyano-amine 3 is treated with methyl magnesium bromide to furnish the methylated derivative 4. The piperidinol 4 is oxidized to the ketone 5 by swern oxididation. The Boc group in 5 is removed by treatment with an acid such as TFA, and the free amine is coupled with acid such as R₃CO₂H using standard conditions to furnish the keto-amide 6. The keto-amide 8 is reacted with a substituted 4-amino piperidine 7 in the presence of sodium triacetoxy borohydride to give the amine 8. The free amine in 8 can be functionalized either by reductive amination (RCHO/Na(AcO)₃BH) or 10 alkylation (NaH or Cs₂CO₃/R²X) to furnish compounds of formula IA.



Compounds of formula IIA where R², R³, R⁴, and M are as defined
15 are prepared according to **Schemes B, C and D** as follows.

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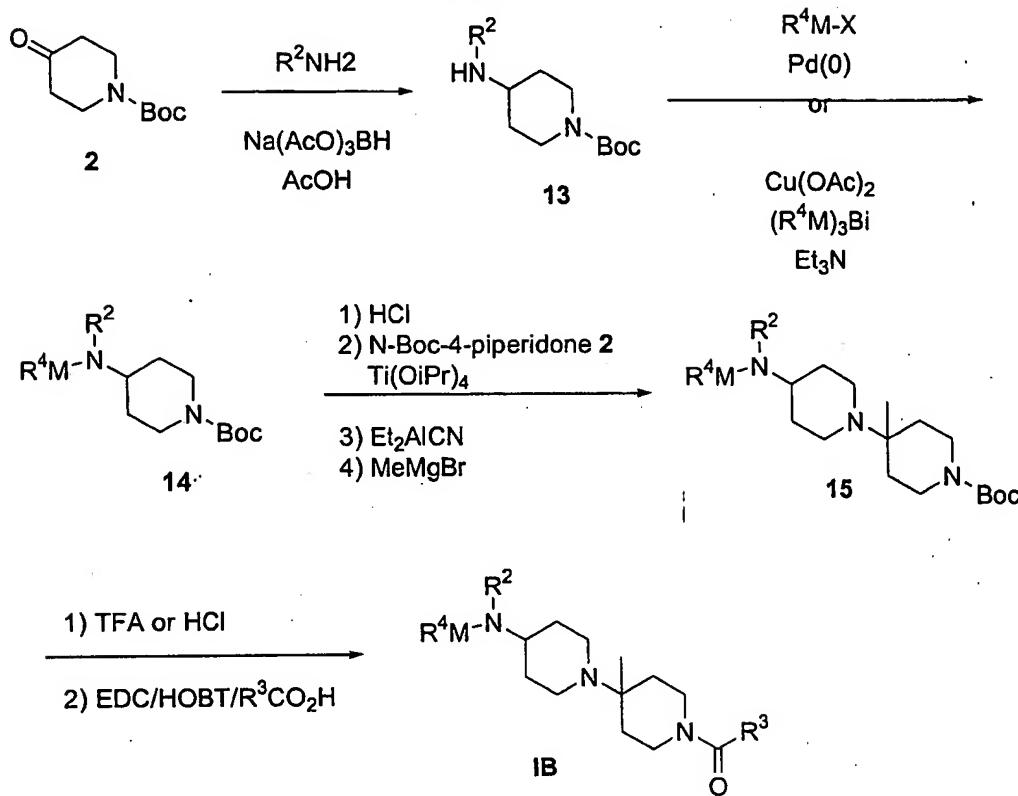
Scheme B

5

The keto-amide **5** is reacted with an amine **10** in the presence of sodium triacetoxyborohydride to furnish the functionalized amine **11**. The amine **11** can be alkylated either with NaH , $\text{Cs}_2\text{CO}_3/\text{R}^2\text{X}$ or $\text{Na}(\text{AcO})_3\text{BH}/\text{RCHO}$ to furnish the tertiary amine **12**. The Boc group in **12** can be removed with an acid such as HCl or TFA, and the resulting piperidine can be coupled to acids to furnish compounds of formula **IB**.

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Scheme C

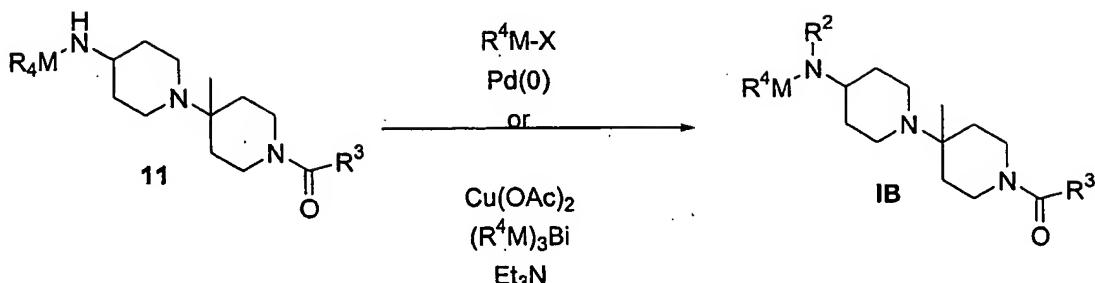
5

N-Boc-4-piperidone **2** is reacted with an amine (R^2NH_2) in the presence of $\text{Na}(\text{AcO})_3\text{BH}$ to furnish the amine **13**. The amine **13** can be reacted with either aryl or heteroaryl halides/triflates under palladium catalysis or $\text{Cu}(\text{OAc})_2/(\text{R}^4\text{M})_3\text{Bi}$ to furnish the arylated amines **14**. The Boc group in **14** can be removed, and the second piperidine ring can be added according to the procedure previously discussed (**Scheme 1**; Steps 1 and 2) to furnish the piperidine **15**. The Boc group in **15** is removed with an acid such as TFA or HCl, and the amine is coupled to an acid represented by $\text{R}_3\text{CO}_2\text{H}$ to furnish the compounds of formula **IB**.

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Scheme D



5

The functionalized amine **11** can be reacted according to procedures outlined above in **Scheme C** to furnish compounds of formula **IB**.

10 For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, 15 cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A.

20 Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

25 Liquid form preparations include solutions, suspensions and emulsions. An example of this includes, but is not limited to, water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

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Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

5 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compound of the invention may also be deliverable
10 transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be deliverable
15 subcutaneously.

Preferably the compound is administered orally.
Preferably, the pharmaceutical preparation is in a unit dosage form.
In such form, the preparation is subdivided into suitably sized unit doses containing a therapeutically effective amount of the compound having
20 formula I.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 10 mg to about 500 mg, preferably from about 25 mg to about 300 mg, more preferably from about 50 mg to about 250 mg, and most preferably from about 55 mg to about 200 mg, according
25 to the particular application.

The actual dosage of the inventive compound employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the
30 total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be

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regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 100 mg/day to about 300
5 mg/day, preferably 150 mg/day to 250 mg/day, more preferably about 200 mg/day, in two to four divided doses.

The doses and dosage regimens of the NRTIs, NNRTIs, PIs and other agents used in combination with the compounds of this invention will be determined by the attending clinician in view of the approved doses and
10 dosage regimens in the package inserts or as set forth in the protocols, taking into consideration the age, sex and condition of the patient and the severity of the condition treated.

In a preferred embodiment, the compound of the present invention can be used to treat Human Immunodeficiency Virus by administering to a
15 patient in need of such treatment a therapeutically effective amount of one or more compounds having formula I, preferably in combination with one or more pharmaceutically acceptable carriers. One or more, preferably one to four, antiviral agents useful in anti-HIV-1 therapy can be used in combination with the compound of the present invention. The antiviral
20 agent or agents can be combined with one or more compounds of the present invention in a single dosage form, or the one or more compounds of the present invention and the antiviral agent or agents may be administered simultaneously or sequentially as separate dosage forms.

The antiviral agents contemplated for use in combination with the
25 compound of the present invention comprise nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and other antiviral drugs listed below not falling within these classifications. Specific examples of antiviral agents include, but are not limited to, zidovudine, lamivudine, zalcitabine,
30 didanosine, stavudine, abacavir, adefovir dipivoxil, lobucavir, BCH-10652, emtricitabine, beta-L-FD4, DAPD, idenosine, nevirapine, delavirdine, efavirenz, PNU-142721, AG-1549, MKC-442, (+)-calanolide A and B, saquinavir, indinavir, ritonavir, nelfinavir, lasinavir, DMP-450, BMS-

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2322623, ABT-378, amprenavir, hydroxyurea, ribavirin, IL-2, IL-12, penta fuside, Yissum No. 11607 and AG-1549. In particular, the combinations known as HAART are contemplated for use in combination with the compound of this invention.

5 For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of the other agent.

10 Another aspect of the invention provides a method of treating solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis comprising administering to a patient in need of such treatment a therapeutically effective amount of one or more

15 compounds of formula I, preferably in combination with one or more pharmaceutically acceptable carriers. In another embodiment, the method for treating solid organ transplant rejection, graft v. host disease, rheumatoid arthritis, inflammatory bowel disease or multiple sclerosis further comprises administering one or more other agents useful in the 20 treatment of said diseases in combination with one or more compounds of formula I.

25 Agents known in the treatment of rheumatoid arthritis, transplant and graft v. host disease, inflammatory bowel disease and multiple sclerosis which can be administered in combination with the compound of the present invention are as follows:

solid organ transplant rejection and graft v. host disease: immune suppressants such as cyclosporine and Interleukin-10 (IL-10), tacrolimus, antilymphocyte globulin, OKT-3 antibody, and steroids;

30 inflammatory bowel disease: IL-10 (see US 5,368,854), steroids and azulfidine;

rheumatoid arthritis: methotrexate, azathioprine, cyclophosphamide, steroids and mycophenolate mofetil;

multiple sclerosis: interferon-beta, interferon-alpha, and steroids.

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Another aspect of the invention relates to a kit comprising in separate containers in a single package pharmaceutical composition for use in combination to treat Human Immunodeficiency Virus. In one container, a pharmaceutical composition comprises one or more compounds of formula I in one or more pharmaceutically acceptable carriers, and in separate containers, one or more pharmaceutical compositions comprising an effective amount of one or more antiviral agents or other agents useful in the treatment of Human Immunodeficiency Virus in one or more pharmaceutically acceptable carriers.

The goal of the HIV-1 therapy of the present invention is to reduce the HIV-1-RNA viral load below the detectable limit. The "detectable limit of HIV-1-RNA" in the context of the present invention means that there are fewer than about 200 to fewer than about 50 copies of HIV-1-RNA per ml of plasma of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HIV-1-RNA is preferably measured in the present invention by the methodology of Amplicor -1 Monitor 1.5 (available from Roche Diagnositics) or of Nuclisens HIV-1 QT -1.

The following assays can be used to determine the CCR5 inhibitory and antagonistic activity of the compounds of the invention.

CCR5 Membrane Binding Assay:

A high throughput screen utilizing a CCR5 membrane binding assay identifies inhibitors of RANTES binding. This assay utilizes membranes prepared from NIH 3T3 cells expressing the human CCR5 chemokine receptor which have the ability to bind to RANTES, a natural ligand for the receptor.

Using a 96-well plate format, membrane preparations are incubated with ^{125}I -RANTES in the presence or absence of compound for one hour. Compounds are serially diluted over a wide range of 0.001ug/ml to 1 ug/ml and tested in triplicates. Reaction cocktails are harvested through glass fiber filters, and washed thoroughly. Total counts for replicates are averaged and data reported as the concentration required to inhibit 50 percent of total ^{125}I -RANTES binding. Compounds with potent activity in the membrane binding assay are further characterized in seconday cell-based HIV-1 entry and replication assays.

HIV-1 Entry Assay:

Replication defective HIV-1 reporter virions are generated by cotransfection of a plasmid encoding the NL4-3 strain of HIV-1 (which has been modified by mutation of the envelope gene and introduction of a luciferase reporter plasmid) along with a plasmid encoding one of several HIV-1 envelope genes as described by Connor et al , *Virology*, 206 (1995), p. 935-944. Following transfection of the two plasmids by calcium phosphate precipitation, the viral supernatants are harvested on day 3 and a functional viral titer determined. These stocks are then used to infect U87 cells stably expressing CD4 and the chemokine receptor CCR5 which have been preincubated with or without test compound. Infections are carried out for 2 hours at 37 °C, the cells washed and media replaced with fresh media containing compound. The cells are incubated for 3 days, lysed and luciferase activity determined. Results are reported as the concentration of compound required to inhibit 50% of the luciferase activity in the control cultures.

HIV-1 Replication Assay:

This assay uses primary peripheral blood mononuclear cells or the stable U87-CCR5 cell line to determine the effect of anti-CCR5 compounds to block infection of primary HIV-1 strains. The primary lymphocytes are purified from normal healthy donors and stimulated *in vitro* with PHA and IL-2 three days prior to infection. Using a 96-well plate format, cells are pretreated with drug for 1 hour at 37 °C and subsequently infected with an M-tropic HIV-1 isolates. Following infection, the cells are washed to remove residual inoculum and cultured in the presence of compound for 4 days. Culture supernatants are harvested and viral replication measured by determination of viral p24 antigen concentration.

Calcium Flux Assay:

Cells expressing the HIV coreceptor CCR5 are loaded with calcium sensitive dyes prior to addition of compound or the natural CCR5 ligand. Compounds with agonist properties will induce a calcium flux signal in the cell, while the compounds of this invention are identified as compounds which do not induce signaling by themselves but are capable of blocking signaling by the natural ligand RANTES.

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GTP S Binding Assay (secondary membrane binding assay):

A GTP S binding assay measures receptor activation by CCR5 ligands. This assay measures the binding of 35 S labeled-GTP to receptor coupled G-proteins that occurs as a result of receptor activation by an appropriate ligand.

5 In this assay, the CCR5 ligand, RANTES, is incubated with membranes from CCR5 expressing cells and binding to the receptor activation (or binding) is determined by assaying for bound 35 S label. The assay quantitatively determines if compounds exhibit agonist characteristics by inducing activation of the receptor or alternatively antagonist properties by measuring inhibition of

10 RANTES binding in a competitive or non-competitive fashion.

Chemotaxis Assay:

The chemotaxis assay is a functional assay which characterizes the agonist vs. antagonist properties of the test compounds. The assay measures the ability of a non-adherent murine cell line expressing human CCR5 (BaF-550) to migrate across a membrane in response to either test compounds or natural ligands (i.e., RANTES, MIP-1 β). Cells migrate across the permeable membrane towards compounds with agonist activity. Compounds that are antagonists not only fail to induce chemotaxis, but are also capable of inhibiting cell migration in response to known CCR5

15 ligands.

Luciferase Replication Assay:

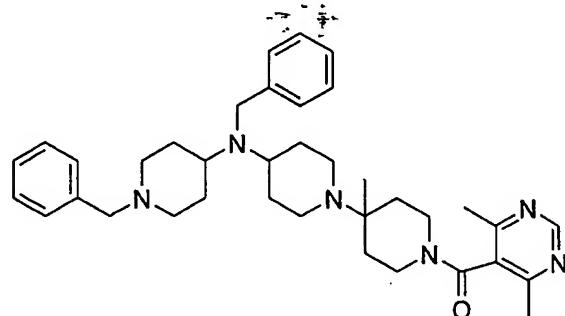
Plasmids encoding the full length genome of HIV-1 pNL-4-Luc with the gp 120 V-3 loop replaced by the Bgl II fragment of HIV-1 ADA, YU-2 or HxB (ADA-Luc-FL, YU-2-Luc-FL and HxB-Luc-FL) are obtained from Dr. Susan Pontow (Washington University, St. Louis MO). Replication-competent luciferase reporter virus stocks are generated by transfection of plasmids into 293T cells using Superfect (Qiagen) or Mirus transfection reagents. Viral stocks are collected 48 hours following transfection and titered for luciferase production on U-87-CCR5 or CXCR4 cells. U87-CD4-
25 CCR5 cells (10^4 /well) are plated in 96-well cell culture plates and incubated overnight. Media is removed and replaced with 50 μ l of fresh culture media
30 (DMEM, 10% FCS) and 50 μ l of compound diluted in culture medium. Cells

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are incubated with compound at 37°C for 1 hour. The resultant supernatant is removed and replaced with 20 µl of media containing compound and infected with an equal volume of diluted or undiluted virus stock at 37 °C for 3-4 hours. The cells are washed once with DMEM, and 200 µl of media containing compound is added. The cultures are incubated for 3 days, the cells lysed in luciferase lysis buffer (Promega, Madison, WI) and transferred to Immulon plates (Dynex Technologies; Chantilly VA). An equal volume of luciferase substrate (Promega, Madison WI) is added to lysates and the plates read immediately in a Wallac Luminometer. Fifty and ninety percent inhibitory concentrations are determined using GraphPad PRISM software.

Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

Example 1:



Compound 4

Step 1

4-Hydroxy-piperidine (1.0 g, 9.9 mmol) and N-Boc-4-piperidone (1.97 g, 9.9 mmol), and Ti(O*i*Pr)₄ (3.2 mL, 10.9 mmol) were taken up in CH₂Cl₂ and stirred at rt for 19 h. To this solution, 24 mL of Et₂AlCN (1.0 M in toluene) were added. The resulting solution was stirred at rt for 24 h. The solution was cooled and quenched with sat. NaHCO₃. The mixture was diluted with EtOAc and filtered through a plug of Celite. The filter cake was rinsed with EtOAc and H₂O. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined EtOAc layers were washed

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with brine and dried (Na_2SO_4). Filtration through Celite and concentration gave a cyanide compound (2.84 g, 93 %) as a solid.

Step 2

The cyanide compound from step 1 (2.84 g, 9.2 mmol) was taken up in THF and cooled to 0°C. Methyl magnesium bromide (15 mL of 3.0 M in diethyl ether) was added to the solution at 0°C. The solution was warmed to rt and stirred at that temperature for 16 h. The solution was cooled to 0°C and quenched with 1 N $\text{NaOH}_{(\text{aq})}$. The mixture was filtered through a plug of Celite. The Celite was rinsed with EtOAc. The aqueous layer was extracted with EtOAc. The combined EtOAc layers were washed with brine and dried (Na_2SO_4). Filtration through Celite and concentration gave an alcohol (2.5 g, 90 %) as an oil.

Step 3

DMSO (0.9 mL, 12.6 mmol) was taken up in CH_2Cl_2 and cooled to –40°C ($\text{CO}_2/\text{CH}_3\text{CN}$). Oxalyl chloride (1.1 mL, 12.6 mmol) was added dropwise to the solution at –40°C. The solution was stirred at that temperature for 20 minutes. The alcohol from step 2 (2.5 g, 8.39 mmol) in CH_2Cl_2 was added to the solution at –40°C. The resulting solution was stirred at that temperature for 30 minutes. Triethyl amine (3.5 mL, 25.2 mmol) was added to the solution at –40°C, and the resulting slurry was warmed to rt. After 30 minutes, the solution was diluted with CH_2Cl_2 and washed with 1 N $\text{NaOH}_{(\text{aq})}$. The aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification via flash chromatography (2/1 EtOAc/hexanes, SiO_2) gave 2.15 grams (87 %) of a ketone as an oil that slowly solidified.

Step 4

Boc-piperidine (2.0 g, 6.7 mmol) was taken up in CH_2Cl_2 and TFA (7 mL) was added. The solution was stirred at rt for 1h. The solution was concentrated. The resulting salt was taken up in H_2O and basified with NaOH. The solution was extracted with CH_2Cl_2 . The aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to furnish 1.1 g (85 %) of deprotected piperidine.

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The deprotected piperidine 1.1 g (5.6 mmol), EDCI hydrochloride (1.6 g), HOBT (1.2 g), diisopropylethylamine (1.8 g), and 4,6-dimethyl-3-pyrimidine carboxylic acid (1.1 g) were taken up in CH₂Cl₂ and stirred at rt for 16 h. The solution was diluted with CH₂Cl₂ and washed with 1 N NaOH_(aq.). The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄. Filtration through Celite and concentration gave 0.94 g (51 %) of amide as a foam.

Step 5:

The amide from step 4 (0.94 g, 2.8 mmol), 4-amino-N-benzyl piperidine (0.5 g), Na(AcO)₃BH (0.84 g), and HOAc (0.26 g) were taken up in CH₂Cl₂ and stirred at rt for 2 h. The solution was diluted with CH₂Cl₂ and washed with 1 N NaOH_(aq.). The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄. Filtration through Celite and concentration gave an oil. Purification via flash chromatography (gradient: CH₂Cl₂-2 % [7 N NH₃ in MeOH] in CH₂Cl₂-4 % [7 N NH₃ in MeOH] in CH₂Cl₂, SiO₂) gave 1.2 g (84 %) of amine as an oil. MS (FAB) 505.4 (MH⁺).

Step 6

The amine from step 5 (0.10 g, 0.20 mmol), benzaldehyde (0.06 g), and Na(AcO)₃BH (0.12 g) were taken up in CH₂Cl₂ and stirred at rt for 15 h. More benzaldehyde (0.06 g) and Na(AcO)₃BH (0.12 g) were added to the reaction. The reaction was stirred for an additional 15 h. The solution was diluted with CH₂Cl₂ and washed with 1 N NaOH_(aq.). The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄. Filtration through Celite and concentration gave an oil. Purification via preparative layer chromatography (7 % [7 N NH₃ in MeOH in CH₂Cl₂, SiO₂]) gave 0.025 g (21 %) of the product shown above in this example. MS (FAB) 595.5 (MH⁺).

The compounds shown below in Table 2 were prepared in a similar fashion as outlined above.

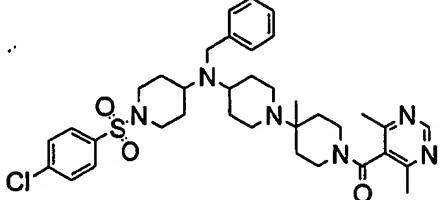
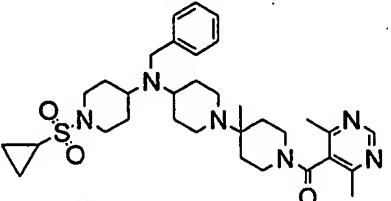
The compounds shown below in Table 2 were prepared in a similar fashion as outlined above for Example 1.

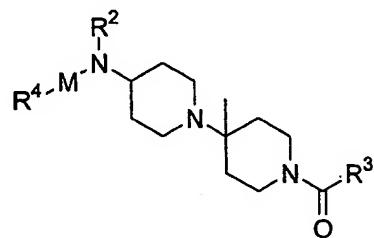
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Table 2

#	<u>Structure</u>	<u>HIV Replication (luciferase) IC50 nM</u>	<u>HRMS found (MH⁺)</u>
1		0.1	679.3197
2		0.8	583.3428
3		32	643.3185
4		1.7	595.4115
5		2.1	679.3184

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6		0.9	679.3181
7		3	609.3598

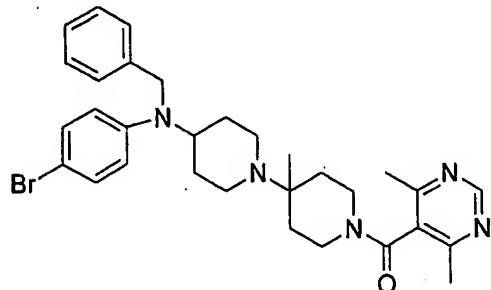


5

This series concentrates on when M = aryl or hetero-aryl. Most preferred are when R² is benzyl, phenyl, and cyclopropylmethyl.

Example 2

10



Compound 8

Step 1

4-Bromo aniline (8.3 g, 48 mmol), N-Boc-4-piperidone (8.0 g, 40 mmol), Na(AcO)₃BH (12.7 g, 60 mmol), and AcOH (3.5 mL, 60 mmol) were

- 51 -

taken up in CH₂Cl₂ and stirred at 25 °C (17 h). The solution was diluted with CH₂Cl₂ and quenched with 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄), filtered and concentrated. Purification via recrystallization
5 (CH₂Cl₂/hexanes) gave 10.2 g (72%) of an amine product.

Step 2

The amine (1.5 g, 4.22 mmol), benzyl bromide (0.74 mL, 6.3 mmol), NaH (250 mg of a 60 wt% dispersion in oil), and KI (350 mg, 2.11) were
10 taken up in DME and stirred at 100 °C (18h). The solution was cooled and partitioned between EtOAc and H₂O. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried (MgSO₄). Filtration and concentration followed by purification via flash chromatography (4/1 hexanes/Et₂O, SiO₂) gave 528 mg (28 %) of a
15 benzyl amine product.

Step 3

The benzyl amine product from step 2 and 4.0 M HCl in dioxane (5 mL) were taken up in MeOH, and the solution was stirred at 25 °C for 18
20 hours. The solution was concentrated. The residue was partitioned between CH₂Cl₂ and 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄. Filtration and concentration gave 314 mg (77 %) of a free amine product.

Step 4

The free amine product from step 3 was treated sequentially with 1) N-Boc-4-piperidone (181 mg, 0.91 mmol)/Ti(O*i*Pr)₄(0.32 mL, 1.1 mmol) and 2) EtAlCN (1.1 mL of a 1.0 M solution in toluene) according to the conditions described above in Step 1 of Example 1. After work-up, 500 mg
30 (Quant.) of a cyano-amine was obtained.

Step 5

- 52 -

The cyano-amine from step 4 was treated with MeMgBr (1.5 mL of a 3.0 M solution in Et₂O) according to the conditions described above in Step 2 of Example 1. Purification via preparative thin-layer chromatography (2/1 hexanes/EtOAc, SiO₂) gave 344 mg (70 %) of the amine as a colorless oil.

5

Step 6

The amine from step 5 and 4.0 M HCl in dioxane (4 mL) were taken up in MeOH and stirred at 25 °C for 17 hours. The solution was concentrated. The HCl salt of the deprotected amine was used as is in the next step.

10

Step 7

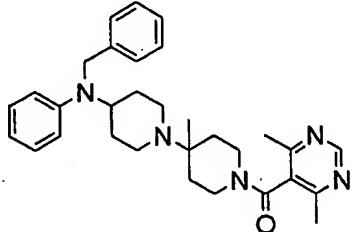
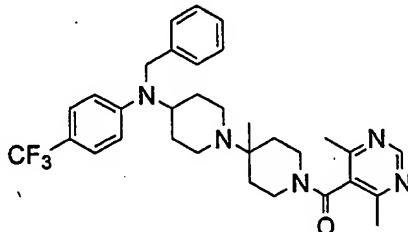
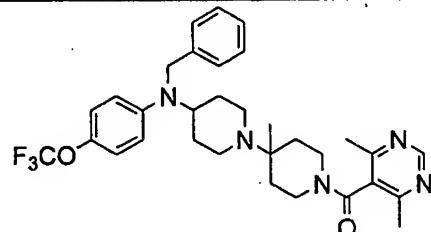
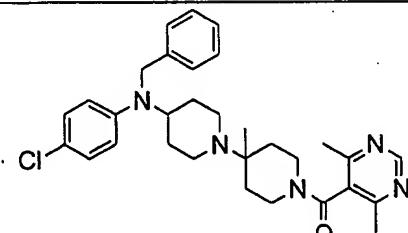
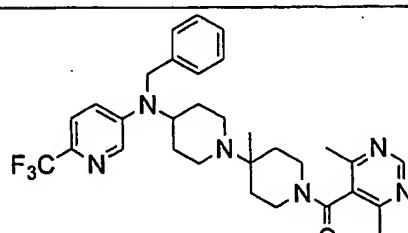
The HCl salt from step 6, EDCI hydrochloride (169 mg, 0.88 mmol), HOBT (119 mg, 0.88 mmol), and iPr₂NEt (1.5 mL, 8.8 mmol), and 4,6-dimethyl-3-pyrimidine carboxylic acid (134 mg, 0.88 mmol) were taken up in CH₃CN and stirred at 25° C for 20 hours. The solution was concentrated. The residue was partitioned between EtOAc and 1 N NaOH. The aqueous layer was extracted with EtOAc. The combined EtOAc layers were washed with brine and dried with Na₂SO₄. Filtration and concentration followed by purification via preparative, thin-layer chromatography (30/1 CH₂Cl₂/7 N NH₃, SiO₂) gave 172 mg (68%) of Compound 8. The amide was taken up in EtOAc and was precipitated as the HCl salt upon addition of 2.0M HCl in Et₂O. m.p.(HCl salt) : 168-170 C. HRMS (MH⁺) calc'd for 576.2338; Found: 576.2331.

20

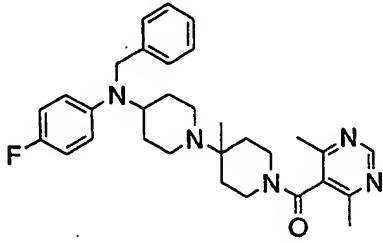
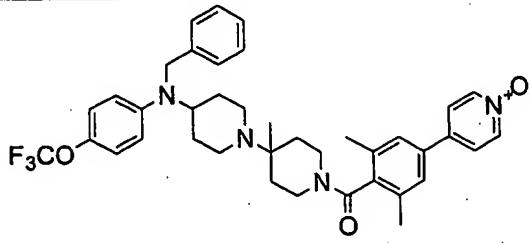
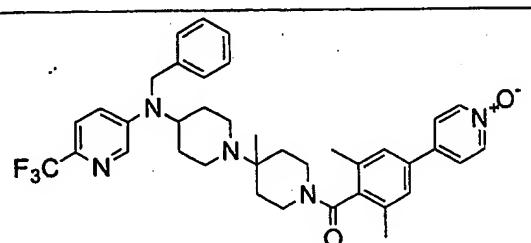
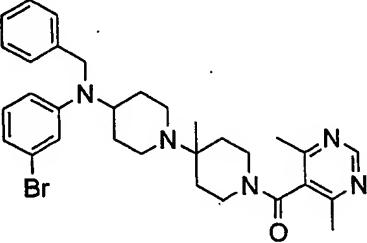
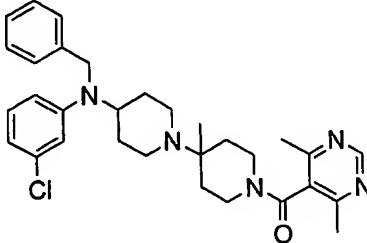
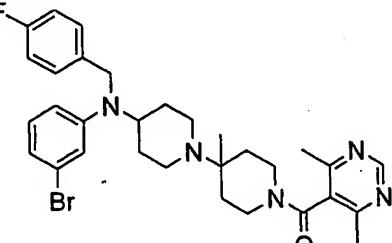
25 The following compounds were prepared via similar procedures:

Table 3

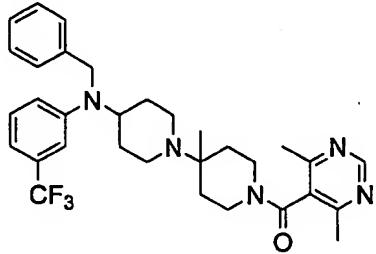
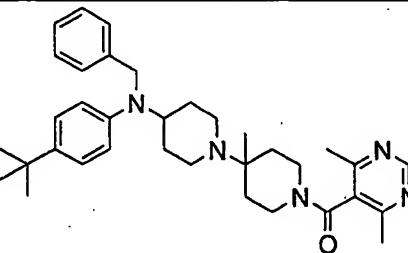
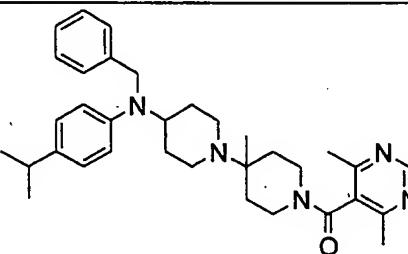
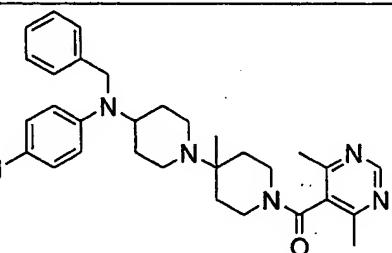
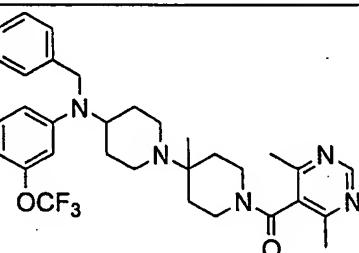
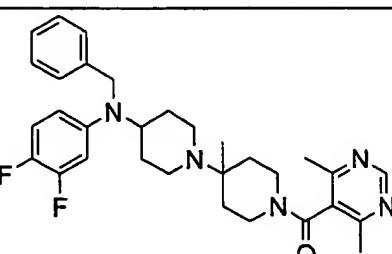
- 53 -

<u>Example</u>	<u>Structure</u>	<u>HIV Replication (luciferase) IC50 nM</u>	<u>HRMS found (MH⁺)</u>
9		3	498.3233
10		0.5	566.3099
11		0.2	582.3064
12		0.2	532.2850
13		0.2	567.3063

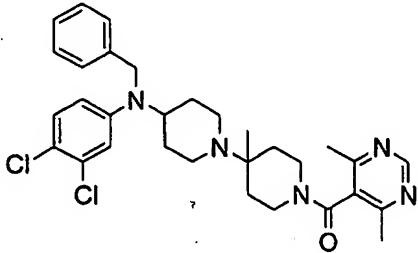
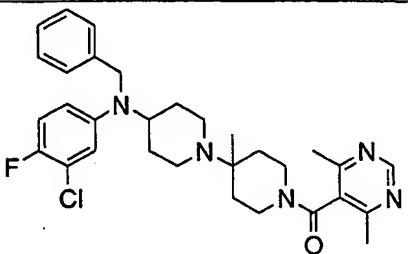
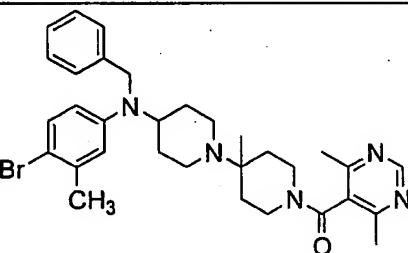
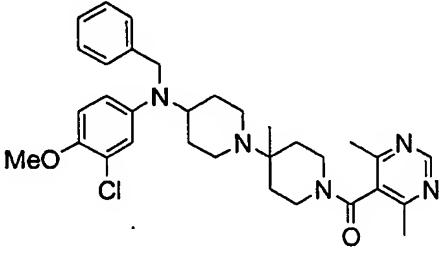
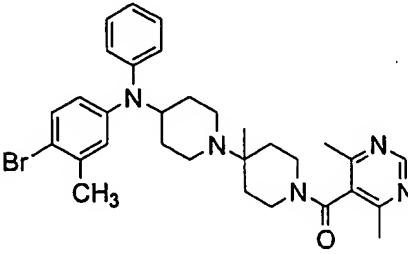
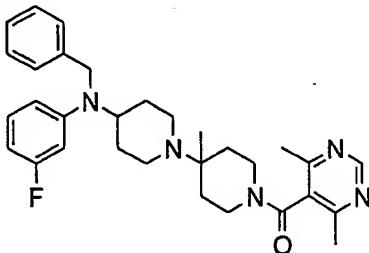
- 54 -

14		0.1	516.3034
15		10	673.3375
16		0.5	658.3377
17		0.1	576.2331
18		0.1	532.2832
19		0.5	594.2235

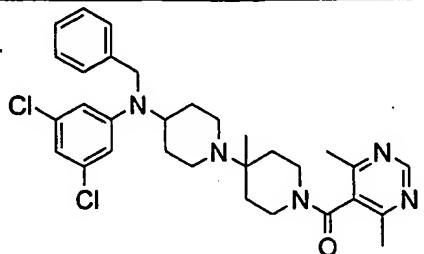
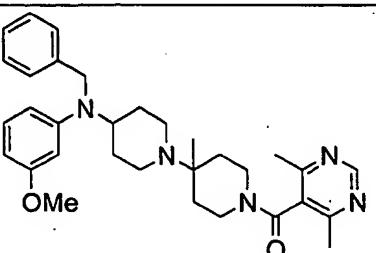
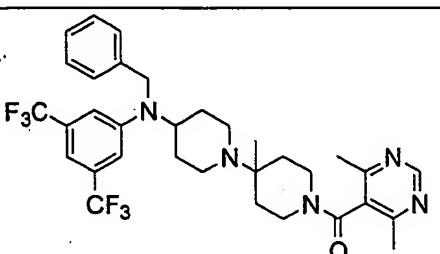
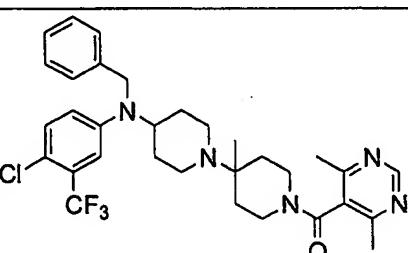
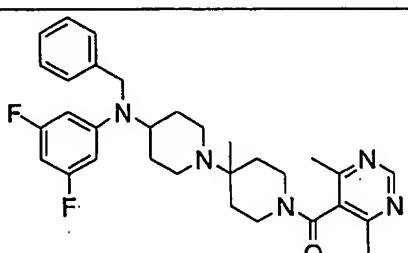
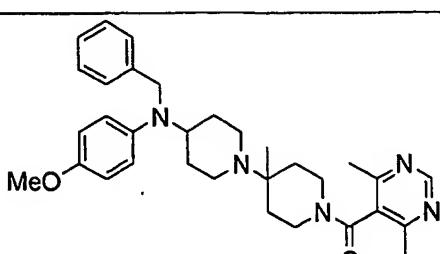
-55-

20		0.2	566.3116
21		1	554.3849
22		0.2	540.3713
23		0.1	624.2203
24		0.2	582.3067
25		0.1	534.3053

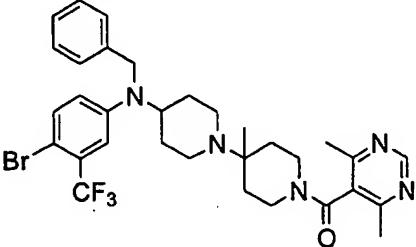
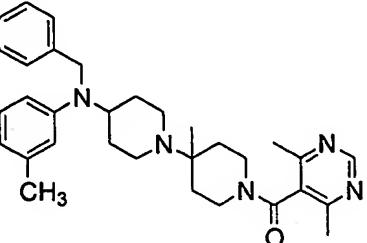
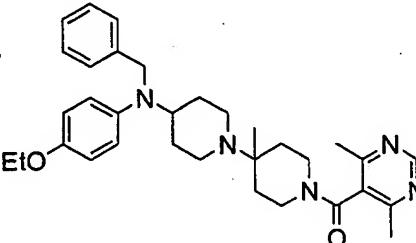
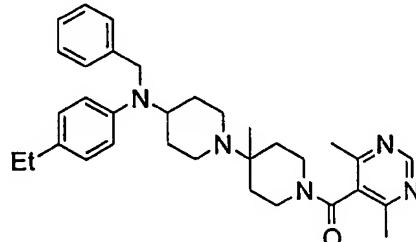
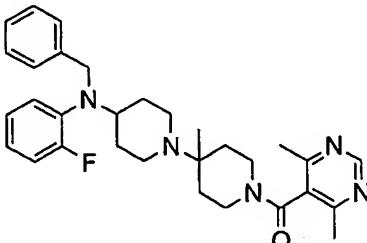
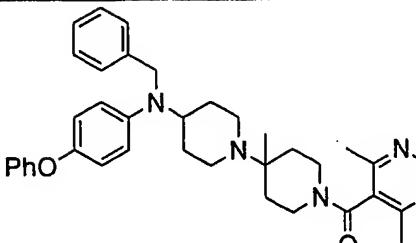
- 56 -

26		0.3	566.2460
27		0.1	550.2753
28		0.22	590.2500
29		0.1	562.2959
30		0.26	578.2314
31		0.44	516.3151

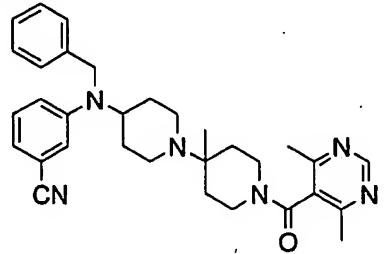
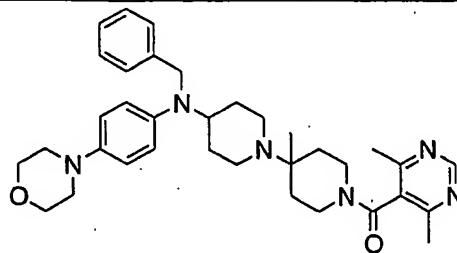
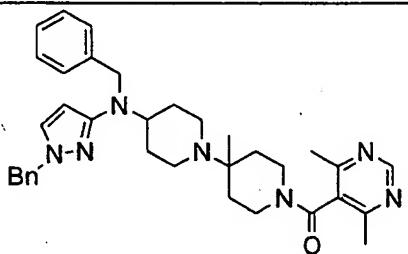
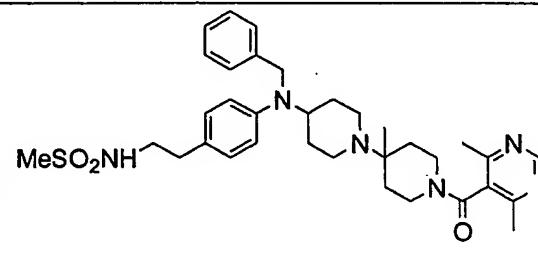
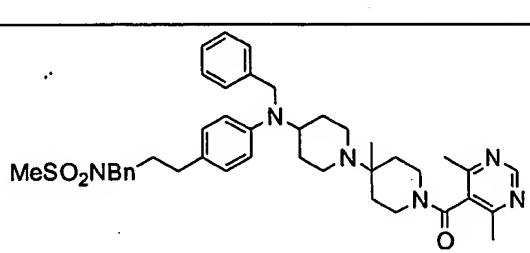
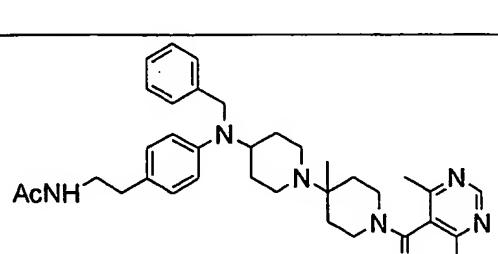
- 57 -

32		1.7	566.2464
33		0.53	528.3349
34		10	634.2993
35		2	600.2712
36		0.1	534.3040
37		0.1	528.3348

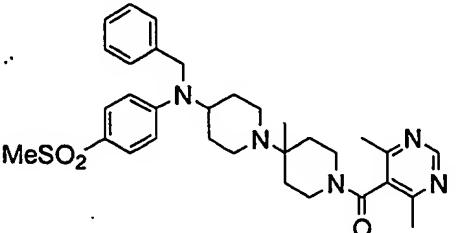
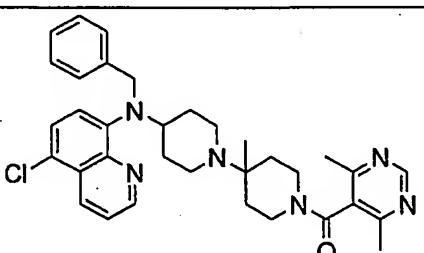
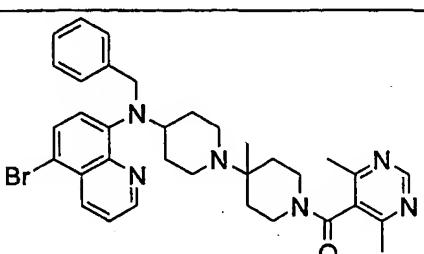
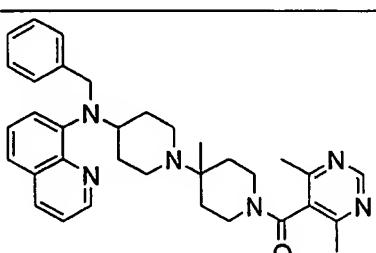
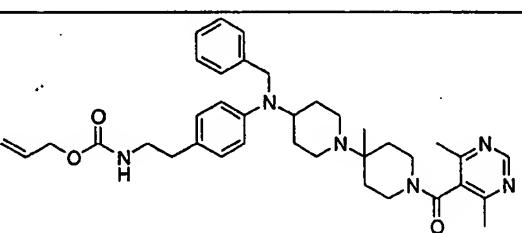
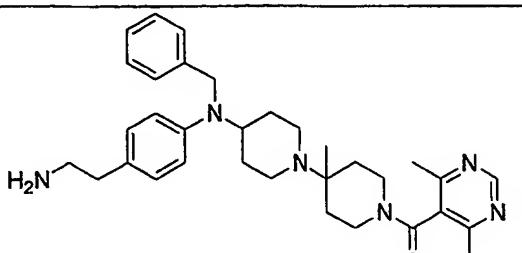
- 58 -

38		3	646.2207
39		0.1	512.3383
40		<0.1	542.3489
41		<0.1	526.3541
42		0.8	516.3142
43		2	590.3502

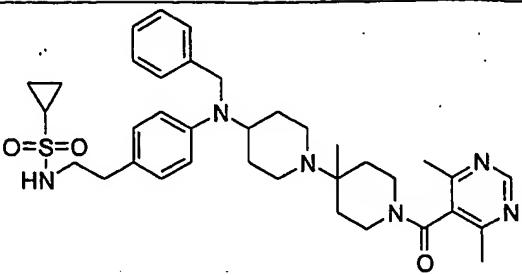
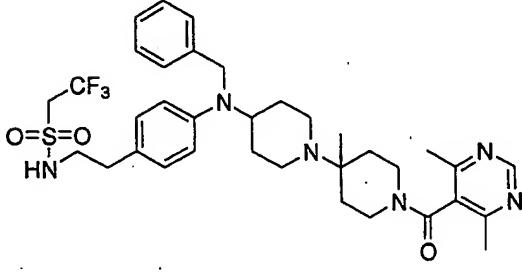
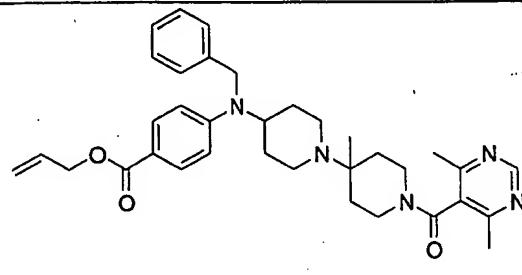
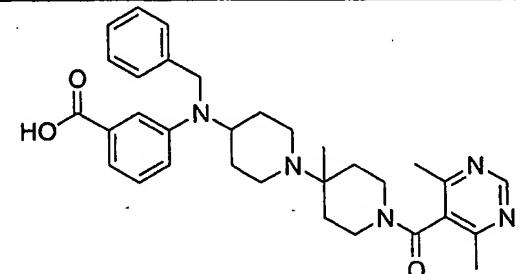
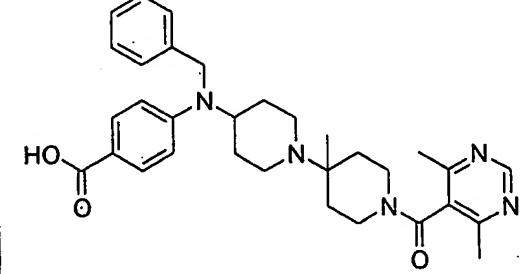
- 59 -

44		0.1	523.3180
45		0.9	538.3765
46		2	578.3603
47		0.05	619.3441
48		0.8	709.3915
49		0.4	583.3756

- 60 -

50		1	576.2998
51		0.32	583.2961
52		1	629.2440
53		0.6	549.3349
54		0.6	625.3853
55		3.5	541.3663

- 61 -

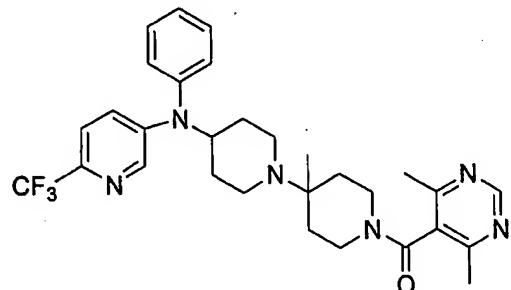
56		0.2	645.3600
57		0.4	687.3323
58		2	582.3459
59		4	542.3118
60		27	542.3136

- 62 -

61		0.5	541.3283
62		4	611.3705
63		6	597.3910
64		4	557.3230
65		2	617.3610

- 63 -

66		1	631.3769
67		6	585.3561
68		2	581.3598

Example 3

Compound 69

Step 1

3-Amino-6-(trifluoromethyl)pyridine (1.0 g, 6.2 mmol), N-Boc-4-piperidone (1.5 g, 7.4 mmol), Na(AcO)₃BH (2.0 g, 9.3 mmol), and AcOH (0.35 mL, 6.2 mmol) were taken up in 1,2-dichloroethane and stirred at 55

- 64 -

°C for 17 hours. The solution was diluted with CH₂Cl₂ and quenched with 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄), filtered and concentrated to furnish a yellow oil. The residue was resubjected to the reaction conditions for 20 hours. After workup, a yellow oil was obtained. The amine product was purified via recrystallization (CH₂Cl₂/hexanes) to give 1.6 g (75%) of the amine.

Step 2

10 The amine from step 1 (500 mg, 1.45 mmol), Ph₃Bi (1.28 g, 2.9 mmol), Cu(OAc)₂ (530 mg, 2.9 mmol), and Et₃N (0.40 mL, 2.9 mmol) were taken up in toluene and heated at 90 °C for 18 hours. More Ph₃Bi, Cu(OAc)₂, and Et₃N were added, and the reaction was stirred at 90 °C (48 h). The solution was filtered through Celite and concentrated. Purification 15 via flash chromatography (3/1 hexanes/EtOAc, SiO₂) gave 352 mg (58%) of the diphenyl amine as a colorless oil.

Steps 3,4,5,6 and 7

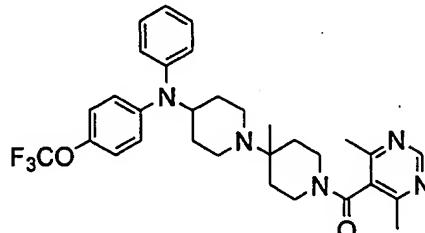
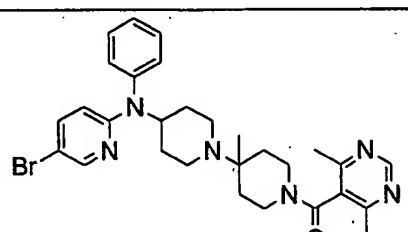
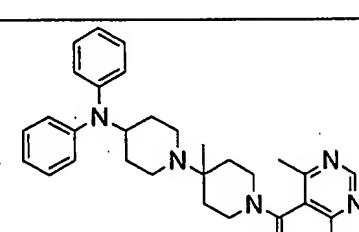
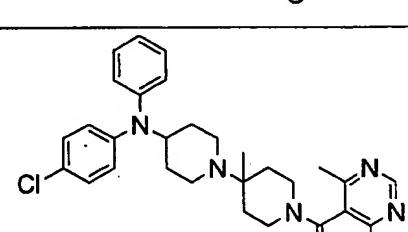
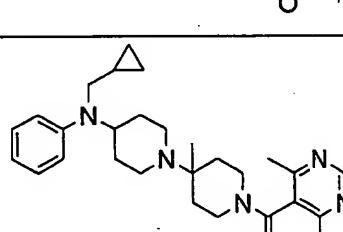
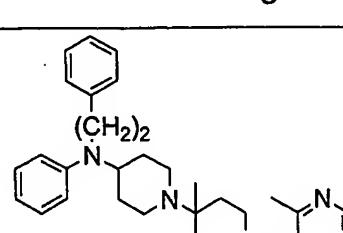
20 The Boc amine from step 2 was converted into the pyrimidine amide following steps 3-7 described above in Example 2AD. Purification via preparative thin layer chromatography (3/1 hexanes/acetone, SiO₂) gave 49 mg of **Compound 69**. HRMS (MH⁺) calc'd for 553.2903: Found, 553.2907. m.p.(HCl): 189-193 C. IC₅₀ = 0.11nm

25 The following compounds were prepared via similar procedures:

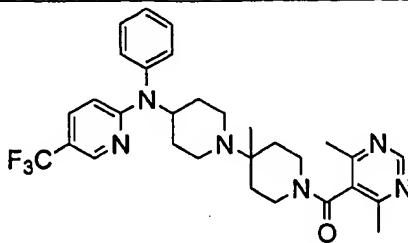
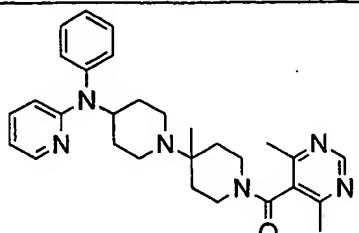
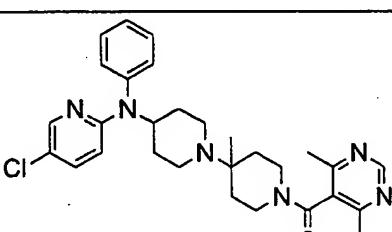
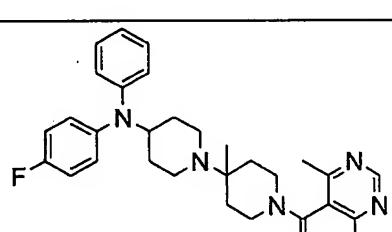
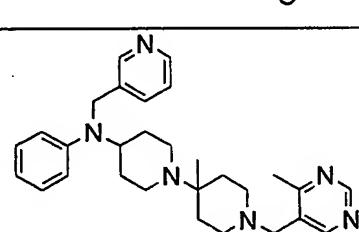
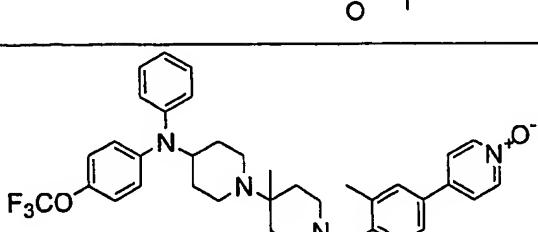
Table 4

Example	SCH	Structure	HIV Replication (luciferase)	HRMS found (MH ⁺)
			IC50 nM	

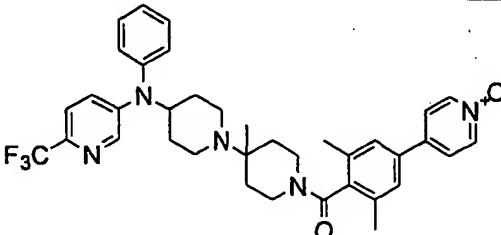
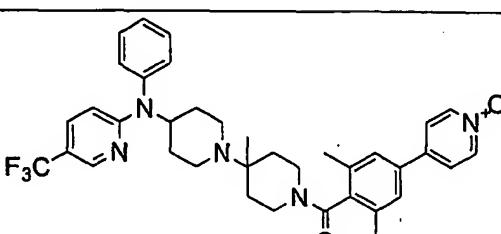
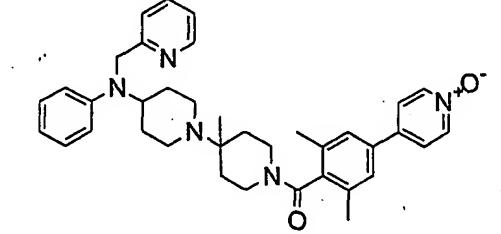
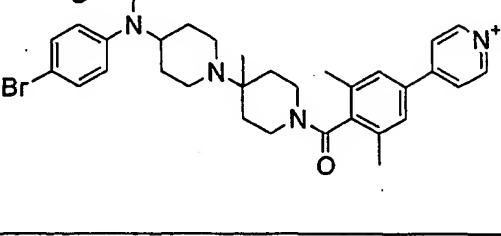
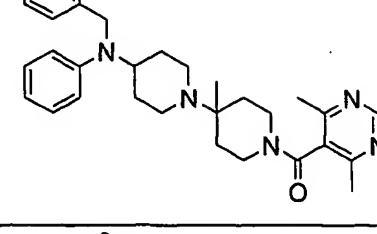
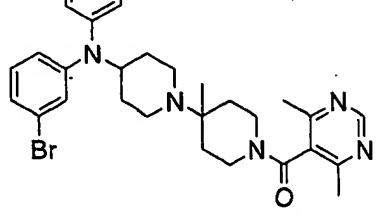
- 65 -

70			1	568.2905
71			0.6	563.2143
72			0.3	484.3080
73			0.3	518.2695
74			10	462.3235
75			38	512.3396

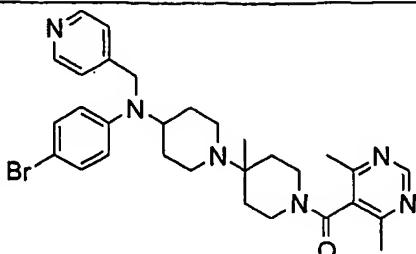
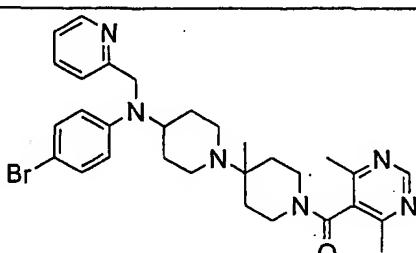
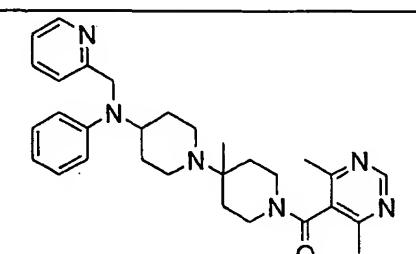
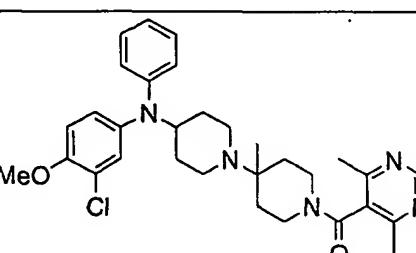
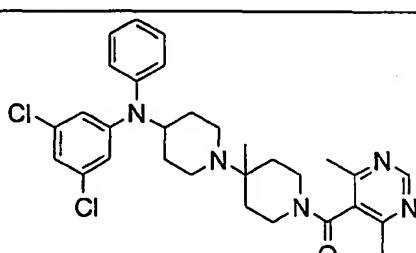
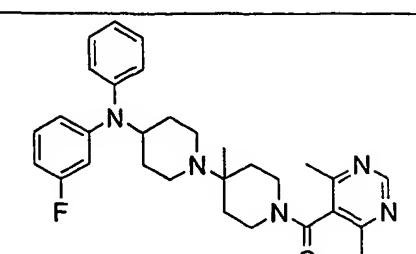
- 66 -

76			0.2	553.2912
77			7	485.3033
78			1	519.2632
79			1	502.2989
80			2	499.3180
81			3	659.3199

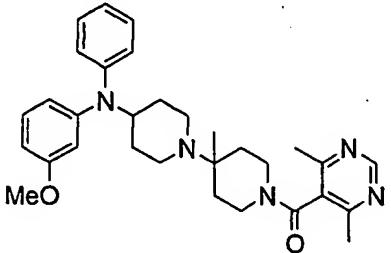
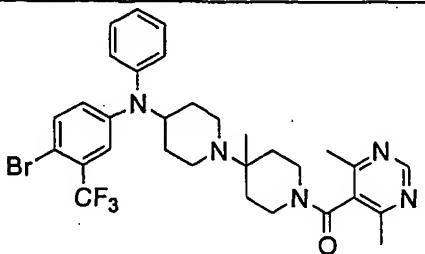
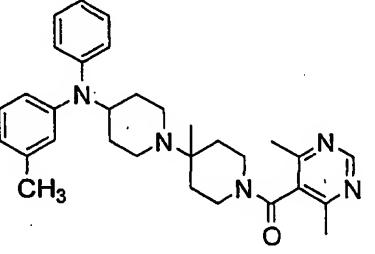
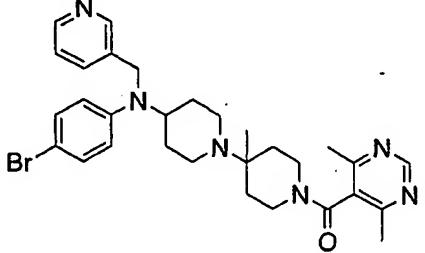
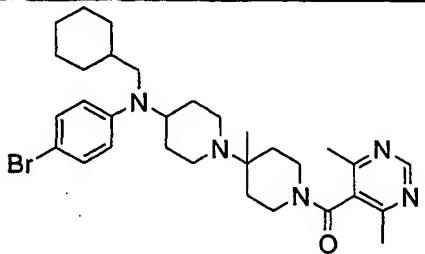
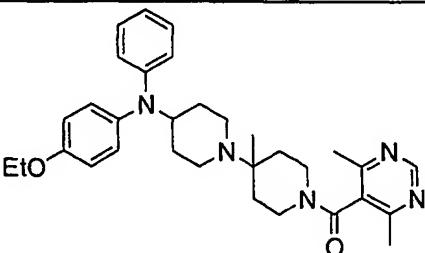
- 67 -

82			0.1	644.3220
83			0.05	644.3226
84			10	590.3490
85			2	504.3696
86			75	499.3193
87			0.1	56202194

- 68 -

88			5	577.2297
89			0.8	577.2286
90			3.4	499.3180
91			0.12	548.2795
92			4.1	552.2293
93			0.21	502.2975

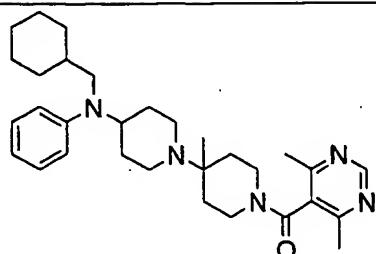
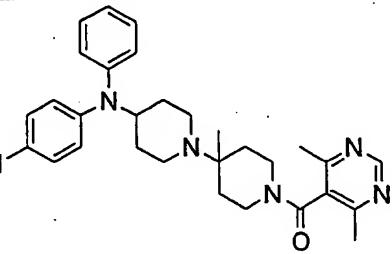
- 69 -

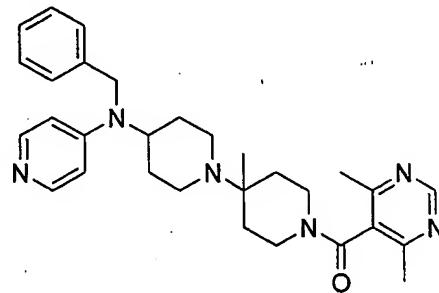
94			1	514.3178
95			2	632.2051
96			0.3	498.3226
97			0.3	579.2271
98			2	582.2808
99			0.3	528.3343

- 70 -

100			0.1	512.3386
101			0.1	520.2890
102			0.3	514.3178
103			2	546.2297
104			3	502.2975
105			5	576.3334

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106			1	504.3696
107			1	610.2057

Example 4

Compound 108

5 Step 1

The ketone 5 (5.0 g, 16.9 mmol), benzyl amine (1.67 mL, 15.3 mmol), $\text{Na}(\text{AcO})_3\text{BH}$ (3.89 g, 18.4 mmol), and AcOH (1.1 mL, 18.4 mL) were taken up in CH_2Cl_2 and stirred at 25 °C for 18 hours. The solution was diluted with CH_2Cl_2 and quenched with 1 N NaOH. The aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried (Na_2SO_4). Filtration and concentration followed by purification via flash chromatography (20/1 CH_2Cl_2 /7 N NH_3 in MeOH, SiO_2) gave 5.79 g (97%) of an amine product.

15 Step 2

The amine from step 1 (200 mg, 0.52 mmol), 4-bromo-pyridine HCl (202 mg, 1.04 mmol), $\text{Pd}(\text{OAc})_2$ (23 mg, 0.1 mmol), $\text{P}(\text{tBu})_3$ (84 mg, 0.42

- 72 -

- mmol), and NaOtBu (200 mg, 2.1 mmol) were taken up in toluene and heated at 110°C for 17 hours. The solution was cooled and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried in Na₂SO₄.
- 5 Filtration and concentration followed by purification via preparative thin-layer chromatography (30/1 CH₂Cl₂/7N NH₃ in MeOH SiO₂) gave 129 mg (54%) of an amino-pyridine product.

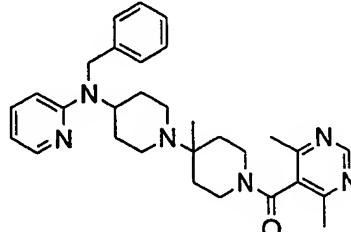
Steps 3 and 4

- 10 The Boc amine from step 2 is treated according to the procedures described above in steps 6 and 7 in Example 2. Purification via preparative thin-layer chromatography (30/1 CH₂Cl₂/7 N NH₃ in MeOH, SiO₂) gave 95 mg (68 %) of an amide product (**Compound 108**). The amide was taken up in EtOAc and was precipitated as the HCl salt upon addition of 2.0M HCl in Et₂O. m.p.(HCl salt) : 182-189 C. HRMS (MH⁺) calc'd for 499.3185; Found: 499.3181. IC₅₀ = 0.8nm
- 15

The following compound was prepared via similar procedures:

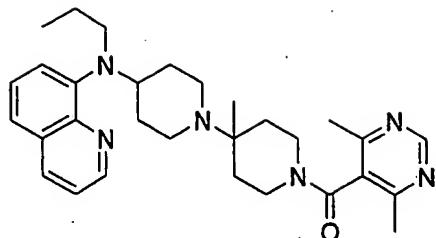
20

Table 5

<u>Example</u>	<u>Structure</u>	<u>HIV Replication (luciferase) IC50 nM</u>	<u>HRMS found (MH⁺)</u>
109		0.3	499.3180

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Example 5



Compound 110

Step1

5 8-Amino quinoline (1.0g, 6.9 mmol), ketone 5 (3.08g, 10.4 mmol), AcOH (1.11mL, 19.3 mmol), and Na(AcO)₃BH (2.9g, 10.4 mmol) were taken up in 30 mL CICH₂CH₂Cl and stirred at 25°C for 16hours. The solution was diluted with CH₂Cl₂ and quenched with 1M NaOH. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers
10 were dried over Na₂SO₄, filtered, and concentrated. The crude product was purified via flash chromatography (gradient 2:1 – 1:1 hexanes/EtOAc) to afford 2.66 g (91%) of an aniline product.

Step 2

15 The aniline (85mg, 0.20 mmol), propanal (23mg, 0.4 mmol), and Na(AcO)₃BH were taken up in CH₂Cl₂ (2 mL). The solution was allowed to stir at 25°C for 16 hours. The solution was diluted with CH₂Cl₂ and quenched with 1M NaOH. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and
20 concentrated to afford 100 mg of a tertiary amine. The product was used without further purification.

Step 3

25 The Boc carbamate and 4.0 M HCl in dioxane (2 mL) were taken up in MeOH (4 mL) and the solution was stirred at 25°C for 3 hours. The solution was concentrated. The HCl salt of the deprotected amine produced here was used as is in the next step.

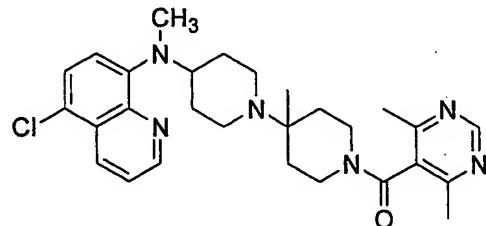
Step 4

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The HCl salt from step 3, EDCI hydrochloride (61 mg, 0.032 mmol), HOBr (43mg, 0.032 mmol), iPr₂Net (0.365 mL, 2.1 mmol), and 4,6-dimethyl-3-pyrimidine carboxylic acid (49 mg, 0.32 mmol) were taken up in MeCN (2 mL) and stirred at 25°C for 24 hours. The solution was concentrated. The residue was partitioned between EtOAc and 1 N NaOH. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄, filtered and concentrated. Purification via preparative, thin-layer chromatography (95/5 CH₂Cl₂/MeOH) gave 60 mg (57%) of an amide product (**Compound 110**). The amide was taken up in EtOAc and was precipitated as the HCl salt upon addition of 2.0 M HCl in Et₂O. m.p. (HCl salt): 181°C (decomposition). HRMS (MH⁺) calc'd 501.3342; found: 501.3349. IC₅₀ = 23nm

Example 6

15



Compound 111

Step 1

8-amino quinoline (4.5g, 31.3 mmol), N-chlorosuccinimide (4.80g, 36 mmol) was taken up in iPrOH (50mL) at 60°C. The mixture was heated to reflux and stirred for 20 min. The solution was cooled to 25°C and concentrated to 1/3 original volume. The mixture was partitioned between CH₂Cl₂ and water. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography (5:1 hexanes/ EtOAc) to afford 1.90 g (34%) of a 8-amino-4-chloro-quinoline product.

Step 2

- 75 -

The quinoline (1.28 g, 7.2 mmol) (3.18g, 10.7 mmol), AcOH (1.16 mL, 20.1mmol), and Na(AcO)₃BH (3.05g, 14.4 mmol) were taken up in 30 mL ClCH₂CH₂Cl and stirred at 25°C for 16 hours. The solution was diluted with CH₂Cl₂ and quenched with 1M NaOH. The aqueous layer was
5 extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The crude product was purified via flash chromatography (2:1 hexanes/EtOAc) to afford 2.0 g (61%) of the quinoline as a yellow oil/foam.

10 Step 3

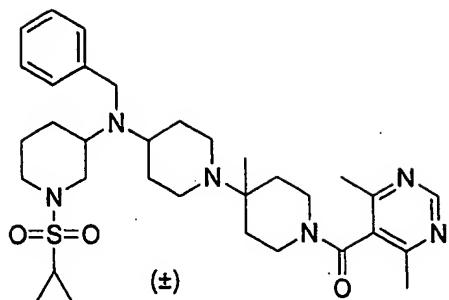
The quinoline from step 2(144mg, 031 mmol), methyl iodide (67mg, 0.47 mmol), and cesium carbonate (153 mg, 0.47 mmol) was taken up in DMF (3 mL) in a sealed tube and heated to 100°C for 24 hours. The mixture was cooled to 25 °C and diluted with EtOAc. The organic layer was
15 washed with water followed by brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude product was purified via preparative, thin-layer chromagotraphy (2:1 hexanes/EtOAc) to afford 14 mg (10%) of a methylated amine product.

20 Step 4

The product of step 3 was treated as described above for Example 5 (steps 3 and 4) to furnish the crude pyrimidine amide. Purification via preparative, thin-layer chromagotraphy (99:1 95/5 CH₂Cl₂/MeOH:7 N NH₃ in MeOH) gave 8 mg (53%) of **Compound 111**. The amide was taken up in
25 EtOAc and was precipitated as the HCl salt upon addition of 2.0 M HCl in Et₂O. m.p. (HCl salt): 164-167°C (decomposition). HRMS (MH⁺) calc'd 507.2639; found: 507.2634.

30 Example 7

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Compound 112

Step 1

5 Compound 108 (10.5 grams) and TFA (20 mL) were taken up in CH₂Cl₂ and stirred at 25 C for 12 hours. The solution was concentrated, and the residue was partitioned between CH₂Cl₂ and 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄). Filtration and concentration gave an amine product.

10

Step 2

The amine from step 1, 4,6-dimethyl-3-pyrimidine carboxylic acid (6 g), EDCI (8.6 g), and iPr₂NEt (7.8 g) were taken up in CH₃CN and stirred at 25 °C for 10 hours. The solution was concentrated, and the residue was partitioned between EtOAc and 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine and dried (Na₂SO₄). Purification via flash chromatography (3%-5% MeOH in CH₂Cl₂, SiO₂) gave 4.9 grams of a pyrimidine-ketone product.

15 Step 3

20 The ketone from step 2 (1.65 g, 4.99 mmol), Na(OAc)₃BH (2.1 g), AcOH (1 g), and (+/-)-3-amino-N-Boc-piperidine (1 g) were taken up in CH₂Cl₂ and stirred at 25 °C for 48 hours. The solution was diluted with CH₂Cl₂ and washed with 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄). Filtration and concentration followed by purification via flash chromatography (3%-10% 7N NH₃ in MeOH/CH₂Cl₂, SiO₂) gave 1.7 g (66%) of an amine product.

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Step 4

The amine from step 3 (400 mg), benzyl bromide (0.2 mL), Cs₂CO₃ (1 g), and KI (10 mg) were heated in DMF at 100 °C for 12 hours. The solution was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried (Na₂SO₄). Filtration and concentration followed by purification via flash chromatography (3% MeOH in CH₂Cl₂, SiO₂) gave 300 mg of a benzyl amine product.

10 Step 5

The amine from step 4 (300 mg) and 4.0M HCl in dioxane (10 mL) were taken up in MeOH and stirred at 25 °C for 10 hours. The solution was concentrated. The residue was partitioned between CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄). Filtration and concentration gave 200 mg of a deprotected amine product.

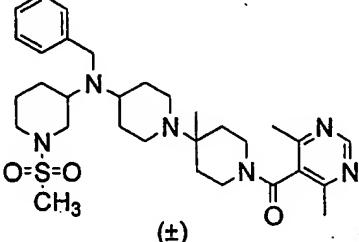
Step 6

The amine from step 5 (100 mg) and cyclopropylsulfonyl chloride (50 mg) were partitioned between CH₂Cl₂ and 1 N NaOH. The mixture was stirred vigorously at 25 °C for 2 h. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄. Filtration and concentration followed by purification via preparative thin-layer chromatography (9 % MeOH in CH₂Cl₂, SiO₂) gave 50 mg of amide product (**Compound 112**). The amide was taken up in EtOAc and was precipitated as the HCl salt upon addition of 2.0M HCl in Et₂O. m.p.(HCl salt) : 190-195 °C. HRMS (MH⁺) calc'd for 609.3587; Found: 609.3578. IC₅₀ = 30nm

30 The following compound was prepared via similar procedures:

Table 6

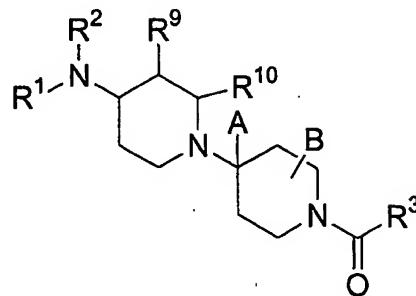
- 78 -

<u>Example</u>	<u>Structure</u>	<u>HIV Replication (luciferase)</u> <u>IC50 nM</u>	<u>HRMS found (MH⁺)</u>
113	 <p style="text-align: center;">(±)</p>	40	583.3422

While the present invention has been described in conjunction with
 5 the specific embodiments set forth above, many alternatives, modifications
 and variations thereof will be apparent to those of ordinary skill in the art.
 All such alternatives, modifications and variations are intended to fall within
 the spirit and scope of the present invention.

WHAT IS CLAIMED:

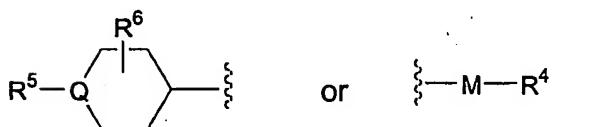
1. A compound represented by the structural formula I



5

or a pharmaceutically acceptable salt or solvate thereof; wherein:

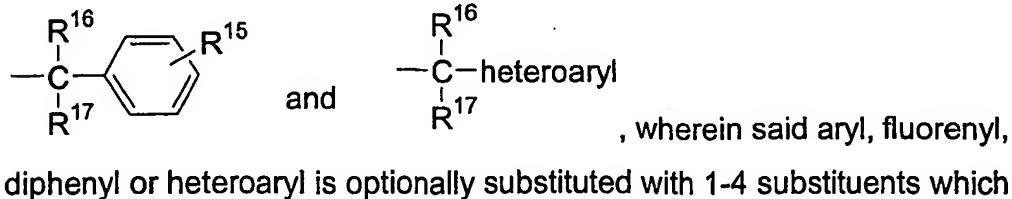
R¹ is



10 R² is selected from the group consisting of H, alkyl, aryl, arylalkyl, heteroarylalkyl, alkylketone, arylketone, alkyl, haloalkyl, cycloalkyl, cycloheteroalkyl, cycloalkylalkyl, alkylsulfonyl, arylsulfonyl, alkoxyalkyl, or amide;

15

 R³ is selected from the group consisting of aryl, 6-membered heteroaryl, fluorenyl; and diphenylmethyl, 6 membered heteroaryl-N-oxide,



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can be the same or different and are independently selected from the group consisting of R¹¹, R¹², R¹³, R¹⁴ and R¹⁵;

R⁴ is 1-3 substituents selected from the group consisting of H, halo, alkyl, haloalkyl, alkoxy, cycloalkyl, cycloheteroalkyl, amide, CF₃, OCF₃, aryl, heteroaryl, -XR⁷, -C(O)C₃-C₈cycloalkyl, -C(O)C₃-C₈cycloheteroalkyl, -(C₁-C₆)alkyl-N(R²¹)SO₂R²², -(C₁-C₆)alkyl-C(O)NR²⁰R²¹, -CN, -CO₂H, -CO₂R²², R⁸-aryl(C₁-C₆)alkyl-, R⁸-heteroaryl(C₁-C₆)alkyl-, -C(O)-(C₁-C₆)alkyl, R⁸-aryl-C(O)-, -C(O)NR²¹R²², -C(O)NH₂, -C(O)N(H)OH, -(C₁-C₆)alkyl-N(R²¹)C(O)R²², -(C₁-C₆)alkyl-N(R²¹)CO₂R²², -(C₁-C₆)alkyl-N(R²¹)C(O)NR²¹R²², -(C₁-C₆)alkyl-NR²¹R²², -(C₁-C₆)alkyl-NH₂, (C₁-C₆)alkylSO₂NR²¹R²² and -SO₂NR²¹R²², wherein R⁴ can be the same or different and is independently selected when there is more than one R⁴ present;

R⁵ is selected from the group consisting of H, arylalkyl, (C₁-C₆)alkyl, R⁸-aryl(C₁-C₆)alkyl-, R⁸-heteroaryl(C₁-C₆)alkyl-, -SO₂-(C₁-C₆)alkyl, -SO₂-(C₃-C₆)cycloalkyl, -SO₂-aryl, R⁸-aryl-SO₂-, -C(O)-(C₁-C₆)alkyl, -C(O)-(C₄-C₆)cycloalkyl, R⁸-aryl-C(O)-, -C(O)NR²¹R²², and -SO₂NR²¹R²²;

R⁶ is H, -(C₁-C₆)alkyl, or -(C₁-C₆)haloalkyl;

R⁷ is selected from the group consisting of aryl, substituted aryl, heteroaryl, alkyl, haloalkyl and cycloalkyl;

R⁸ is 1, 2 or 3 substituents selected from the group consisting of H, halo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -CF₃, -OCF₃, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂- and -NH₂, wherein R⁸ can be the same or different and is independently selected when there are more than one R⁸ present;

R⁹, R¹⁰ and B can be the same or different and are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, and -(C₁-C₆)haloalkyl;

R¹¹ and R¹² can be the same or different and are each independently selected from the group consisting of (C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, halogen, -NR¹⁹R²⁰, -OH, CF₃, -OCH₃, -O-acyl, and -OCF₃;

R¹³ is selected from the group consisting of hydrogen, R¹¹, H, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR₁₉, pyridyl-N-oxide, pyrimidinyl, pyrazinyl, N(R₂₀)CONR₂₀R₂₁, -NHCONH(chloro-(C₁-C₆)alkyl), -

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NHCONH((C₃-C₁₀)-cycloalkyl(C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHCOCF₃, -NSO₂N((C₁-C₆)alkyl)₂, -NSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, (C₃-C₁₀)cycloalkyl, -SR²², -SOR²², -SO₂R²², -SO₂NH(C₁-C₆)alkyl, -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CONR¹⁹R²⁰, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R₁₉, -Si(CH₃)₃ and -B(OC(CH₃)₂)₂;

5 R¹⁴ is selected from the group consisting of (C₁-C₆)alkyl, -(C₁-C₆)haloalkyl -NH₂ and R¹⁵-phenyl;

10 R¹⁵ is 1-3 substituents selected from the group consisting of hydrogen, (C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, -CF₃, -CO₂R²⁰, -CN, (C₁-C₆)alkoxy and halogen; wherein R¹⁵ can be the same or different and is independently selected when there are more than one R¹⁵ present;

15 R¹⁶ and R¹⁷ can each be the same or different and are each independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl, or

R¹⁶ and R¹⁷ together are a C₂-C₅ alkylene group and with the carbon to which they are attached from a spiro ring of 3 to 6 carbon atoms;

20 R¹⁹, R²⁰ and R²¹ can each be the same or different and are each independently selected from the group consisting of H, (C₁-C₆)alkyl and (C₃-C₆)cycloalkyl;

25 R²² is selected from the group consisting of (C₁-C₆)alkyl, -(C₁-C₆)haloalkyl, (C₂-C₆)hydroxyalkyl, (C₂-C₆)alkylene, (C₃-C₆)cycloalkyl, aryl and aryl(C₁-C₆)alkyl-;

A is selected from the group consisting of H, (C₁-C₆)alkyl, and (C₂-C₆) alkenyl.

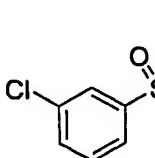
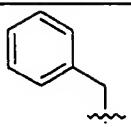
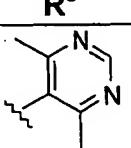
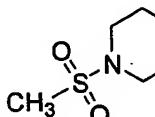
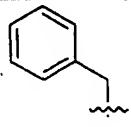
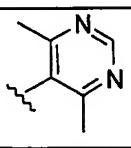
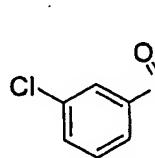
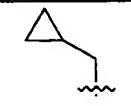
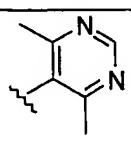
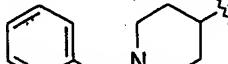
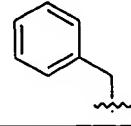
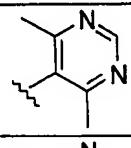
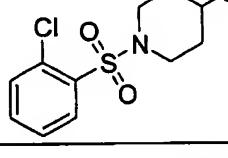
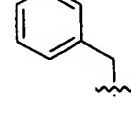
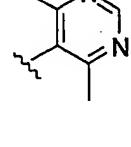
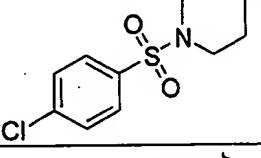
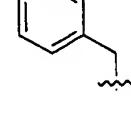
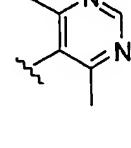
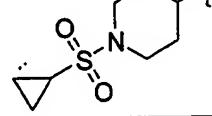
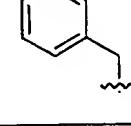
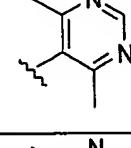
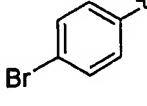
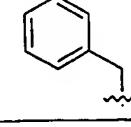
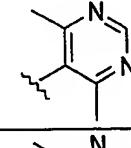
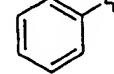
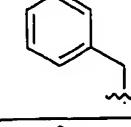
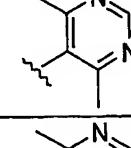
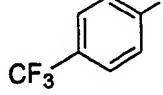
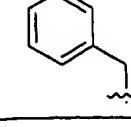
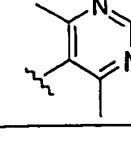
M is aryl or heteroaryl optionally substituted with R⁴;

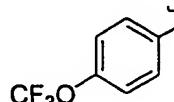
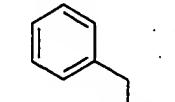
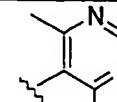
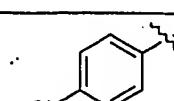
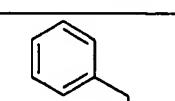
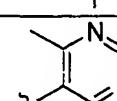
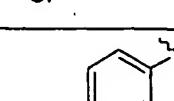
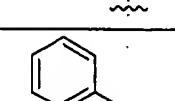
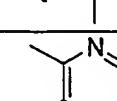
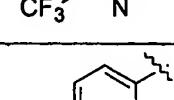
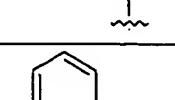
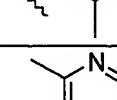
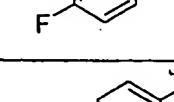
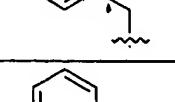
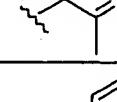
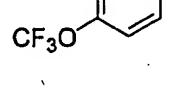
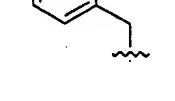
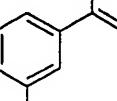
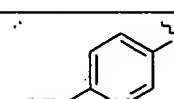
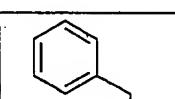
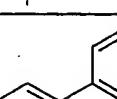
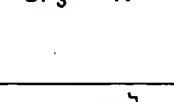
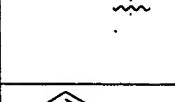
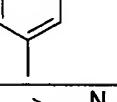
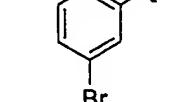
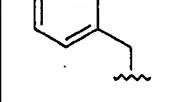
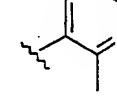
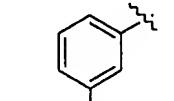
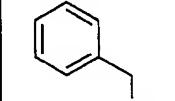
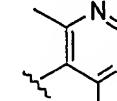
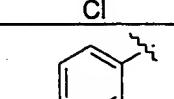
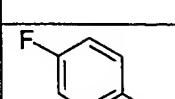
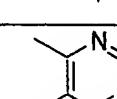
Q is CH or N; and

X is selected from the group consisting of CH₂, SO₂, SO, S, and O, with the following proviso:

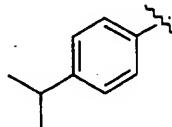
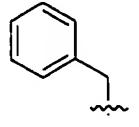
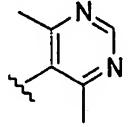
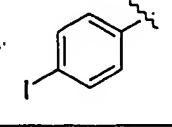
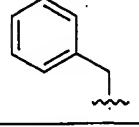
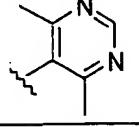
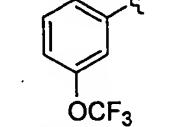
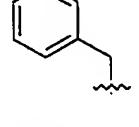
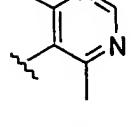
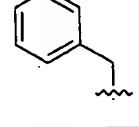
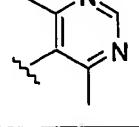
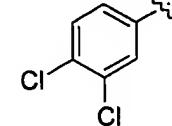
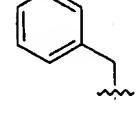
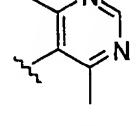
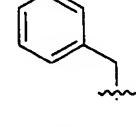
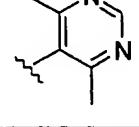
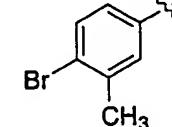
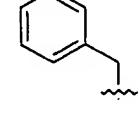
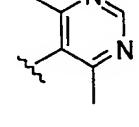
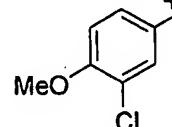
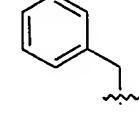
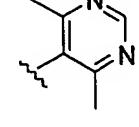
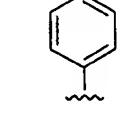
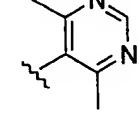
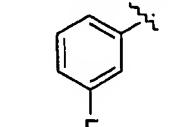
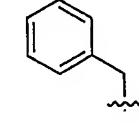
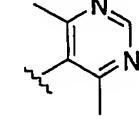
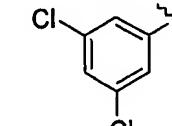
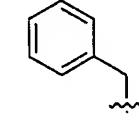
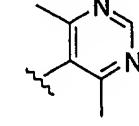
30 when R¹ is phenyl, pyridyl, thiophenyl or naphthyl, R² cannot be H, -(C₁-C₆)alkyl or -C(O)-(C₁-C₆)alkyl.

2. A compound having the structural formula I according to claim 1 wherein R⁹, R¹⁰ and B are H, and R¹, R² and R³ are as defined in the following table:

#	R ¹	R ²	R ³
1			
2			
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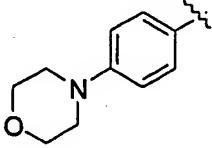
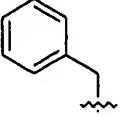
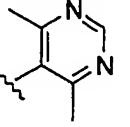
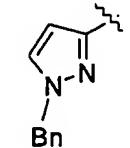
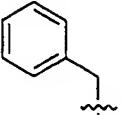
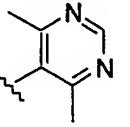
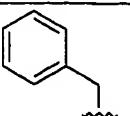
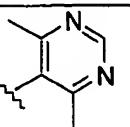
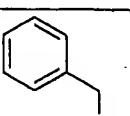
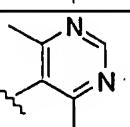
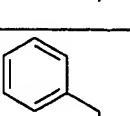
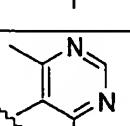
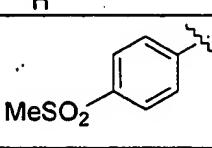
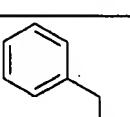
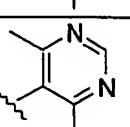
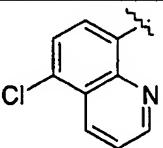
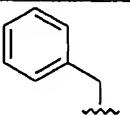
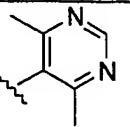
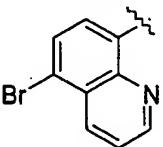
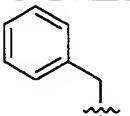
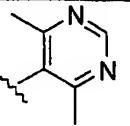
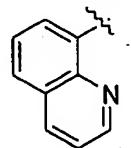
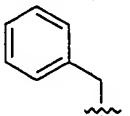
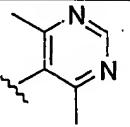
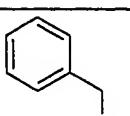
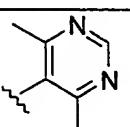
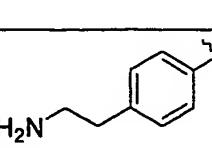
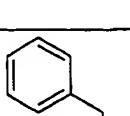
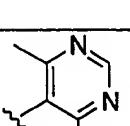
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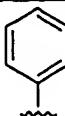
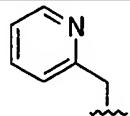
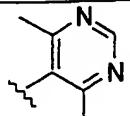
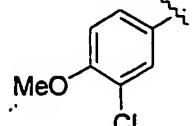
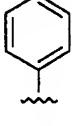
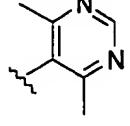
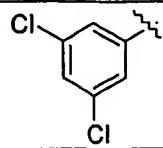
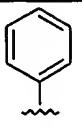
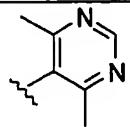
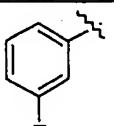
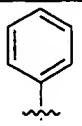
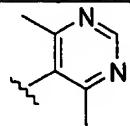
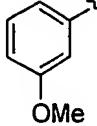
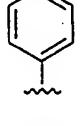
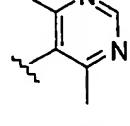
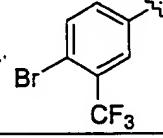
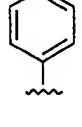
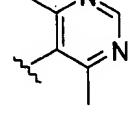
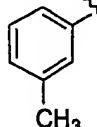
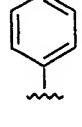
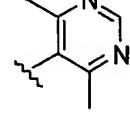
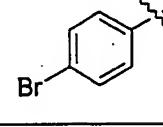
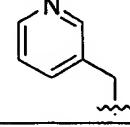
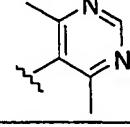
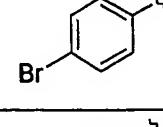
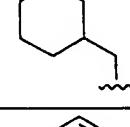
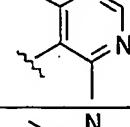
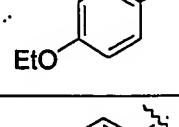
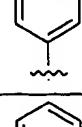
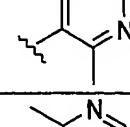
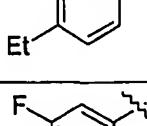
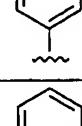
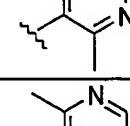
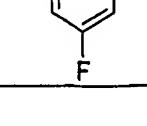
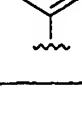
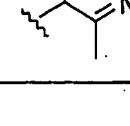
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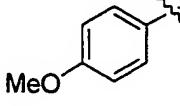
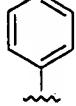
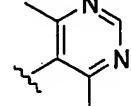
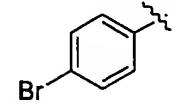
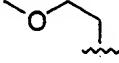
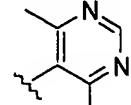
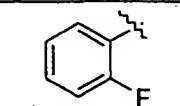
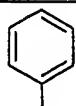
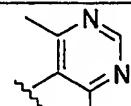
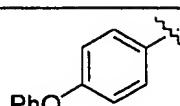
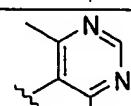
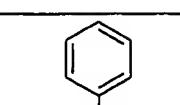
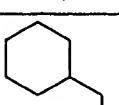
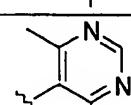
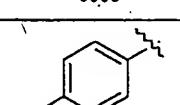
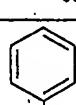
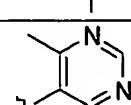
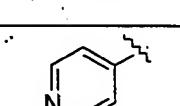
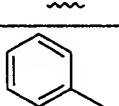
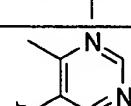
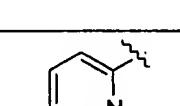
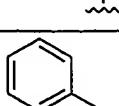
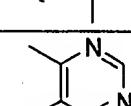
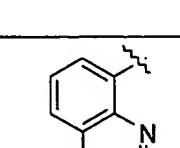
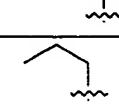
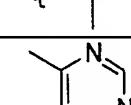
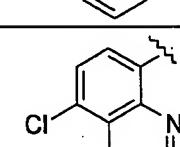
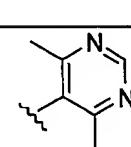
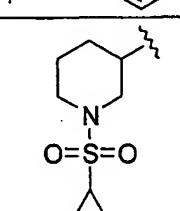
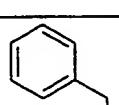
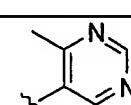
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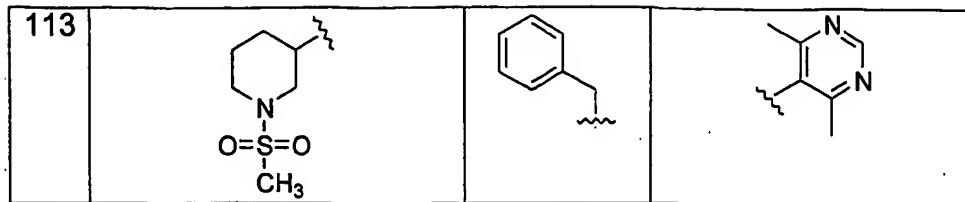
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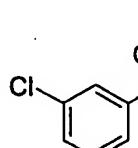
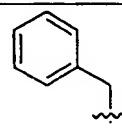
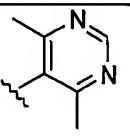
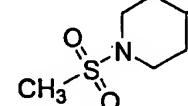
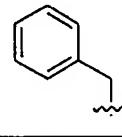
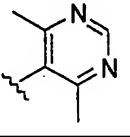
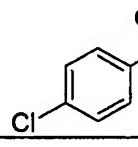
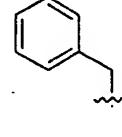
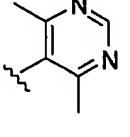
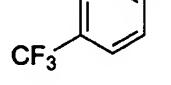
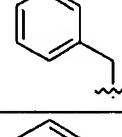
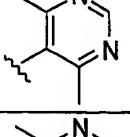
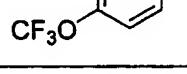
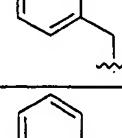
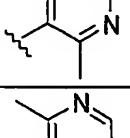
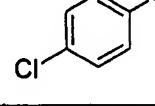
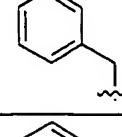
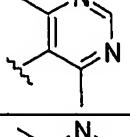
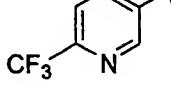
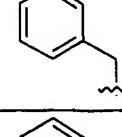
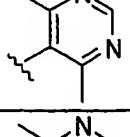
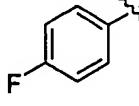
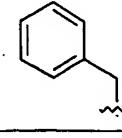
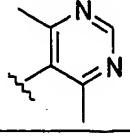
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3. A compound according to claim 2 wherein R¹, R² and R³ each represent:

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16	<chem>C(F)(F)c1cc(C)cnc1</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2[N+](=O)[O-]</chem>
17	<chem>Cc1ccccc1Br</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2</chem>
28	<chem>Cc1ccccc1BrC</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2</chem>
29	<chem>Cc1ccccc1ClO</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2</chem>
31	<chem>Cc1ccccc1F</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2</chem>
36	<chem>Cc1cc(F)cc(F)cc1</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2</chem>
37	<chem>Cc1ccccc1O</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2</chem>
39	<chem>Cc1ccccc1C</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2</chem>
40	<chem>Cc1ccccc1OCC</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2</chem>
47	<chem>CN(c1ccccc1)S(=O)(=O)Cc2ccccc2</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2</chem>
49	<chem>CN(C)Cc2ccccc2</chem>	<chem>Cc1ccccc1</chem>	<chem>Cc1ccccc1Cc2ccncc2</chem>

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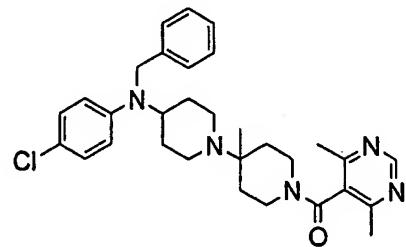
50	<chem>*c1ccc(cc1)C(=O)NCCCS(=O)(=O)c2ccccc2</chem>	<chem>*c1ccc(cc1)Cc2ccccc2</chem>	<chem>*c1ccc(cc1)C(=O)c2ccnnc2</chem>
56	<chem>*c1ccc(cc1)C(=O)NCCCS(=O)(=O)c2ccccc2</chem>	<chem>*c1ccc(cc1)Cc2ccccc2</chem>	<chem>*c1ccc(cc1)C(=O)c2ccnnc2</chem>
57	<chem>*c1ccc(cc1)C(=O)NCCCS(=O)(=O)c2ccccc2</chem>	<chem>*c1ccc(cc1)Cc2ccccc2</chem>	<chem>*c1ccc(cc1)C(=O)c2ccnnc2</chem>
61	<chem>*c1ccc(cc1)C(=O)Nc2ccccc2</chem>	<chem>*c1ccc(cc1)Cc2ccccc2</chem>	<chem>*c1ccc(cc1)C(=O)c2ccnnc2</chem>
68	<chem>*c1ccc(cc1)C(=O)NC2CC2</chem>	<chem>*c1ccc(cc1)Cc2ccccc2</chem>	<chem>*c1ccc(cc1)C(=O)c2ccnnc2</chem>
69	<chem>*c1ccc(cc1)C(F)(F)F</chem>	<chem>*c1ccc(cc1)Cc2ccccc2</chem>	<chem>*c1ccc(cc1)C(=O)c2ccnnc2</chem>
70	<chem>*c1ccc(cc1)C(F)(F)OC(F)(F)F</chem>	<chem>*c1ccc(cc1)Cc2ccccc2</chem>	<chem>*c1ccc(cc1)C(=O)c2ccnnc2</chem>
71	<chem>*c1ccc(cc1)Br</chem>	<chem>*c1ccc(cc1)Cc2ccccc2</chem>	<chem>*c1ccc(cc1)C(=O)c2ccnnc2</chem>
80	<chem>*c1ccc(cc1)C(F)(F)F</chem>	<chem>*c1ccc(cc1)Cc2ccncc2</chem>	<chem>*c1ccc(cc1)C(=O)c2ccnnc2</chem>
81	<chem>*c1ccc(cc1)C(F)(F)OC(F)(F)F</chem>	<chem>*c1ccc(cc1)Cc2ccccc2</chem>	<chem>*c1ccc(cc1)C(F)(F)OC(F)(F)F</chem>
82	<chem>*c1ccc(cc1)C(F)(F)F</chem>	<chem>*c1ccc(cc1)Cc2ccccc2</chem>	<chem>*c1ccc(cc1)C(F)(F)OC(F)(F)F</chem>

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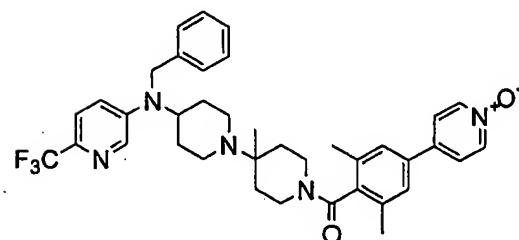
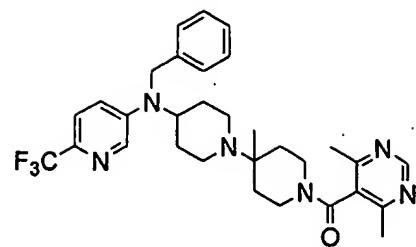
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4. A compound according to claim 3 represented by the structural formulae:

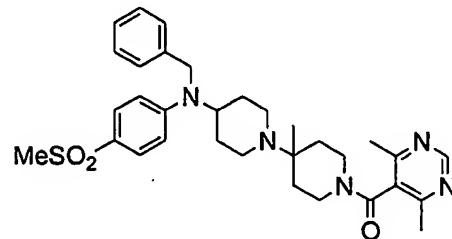
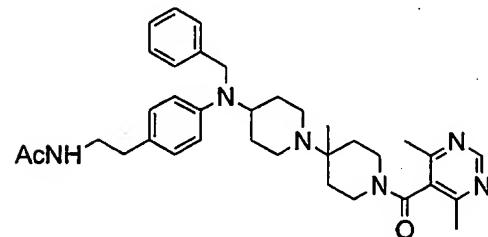
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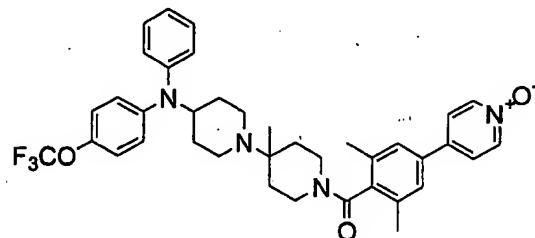
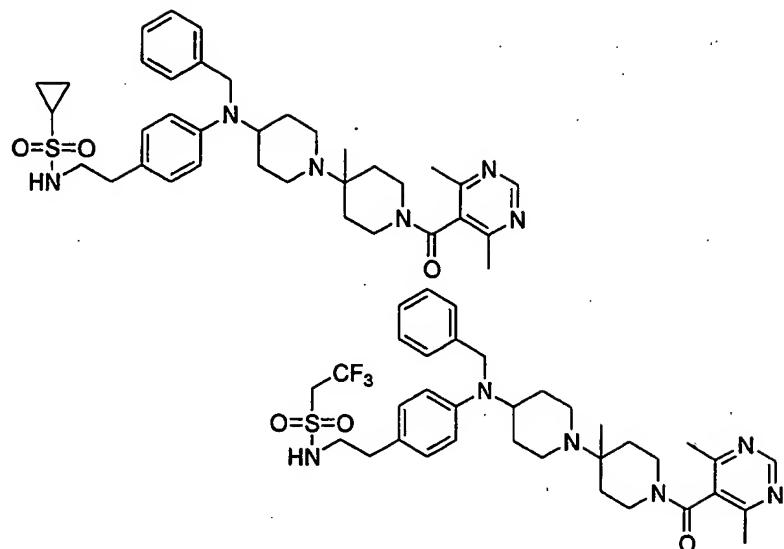


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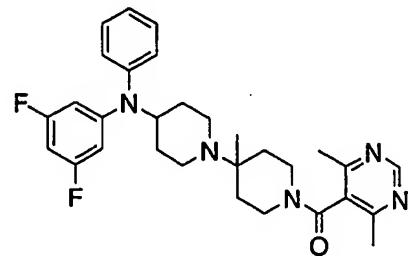
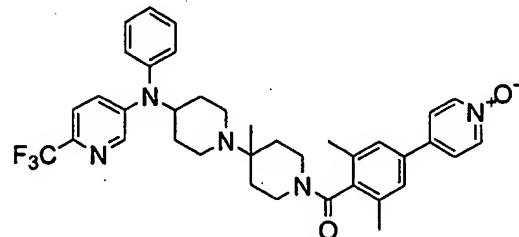


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5. A pharmaceutical composition comprising one or more compounds of claim 1.

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6. A pharmaceutical composition comprising one or more compounds of claim 4
7. The pharmaceutical composition according to claim 5 further comprising one or more pharmaceutically acceptable carriers.
8. The pharmaceutical composition according to claim 6 further comprising one or more pharmaceutically acceptable carriers.
- 10 9. The pharmaceutical composition according to claim 5, wherein said pharmaceutical composition contains a therapeutically acceptable amount of said one or more compounds.
10. The pharmaceutical composition according to claim 6, wherein said pharmaceutical composition contains a therapeutically acceptable amount of said one or more compounds.
11. A method of treating Human Immunodeficiency Virus comprising administering to a patient in need of such treatment a therapeutically effective amount of one or more compounds according to claim 1.
12. A method of treating Human Immunodeficiency Virus comprising administering to a patient in need of such treatment a therapeutically effective amount of one or more compounds according to claim 4.
- 25 13. The method of claim 12 further comprising administering said one or more compounds in combination with one or more pharmaceutically acceptable carriers.
- 30 14. The method of claim 12 further comprising administering one or more antiviral or other agents useful in the treatment of Human Immunodeficiency Virus in combination with said one or more compounds according to claim 1.

15. The method of claim 14 wherein said antiviral agent is selected from the group consisting of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

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16. The method of claim 14 wherein said antiviral agent is selected from the group consisting of zidovudine, lamivudine, zalcitabine, didanosine, stavudine, abacavir, adefovir dipivoxil, lobucavir, BCH-10652, emtricitabine, beta-L-FD4, DAPD, Idenosine, nevirapine, delavirdine, 10 efavirenz, PNU-142721, AG-1549, MKC-442, (+)-calanolide A and B, saquinavir, indinavir, ritonavir, nelfinavir, lasinavir, DMP-450, BMS-2322623, ABT-378, amprenavir, hydroxyurea, ribavirin, IL-2, IL-12, penta fuside, Yissum No. 11607 and AG-1549.

15 17. A method of treating solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis comprising administering to a patient in need of such treatment a therapeutically effective amount of one or more compounds of claim 1

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18. The method of claim 17 for treating solid organ transplant rejection, graft v. host disease, rheumatoid arthritis, inflammatory bowel disease or multiple sclerosis further comprising administering said one or more compounds in combination with one or more pharmaceutically acceptable 25 carriers.

19. The method of claim 17 for treating solid organ transplant rejection, graft v. host disease, rheumatoid arthritis, inflammatory bowel disease or multiple sclerosis further comprising administering one or more other 30 agents useful in the treatment of said diseases in combination with said one or more compounds of claim 1.

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20. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat Human Immunodeficiency Virus which comprises in one container a pharmaceutical composition comprising one or more compounds of claim 1 in one or more pharmaceutically acceptable carriers, and in separate container, one or more pharmaceutical compositions comprising one or more antiviral or other agents useful in the treatment of Human Immunodeficiency Virus in one or more pharmaceutically acceptable carriers.
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/27389

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 A61P31/18 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 01425 A (SCHERING CORP) 15 January 1998 (1998-01-15) claims 1,7	1-10
X	US 5 952 349 A (GREEN MICHAEL J ET AL) 14 September 1999 (1999-09-14) claims 1,10	1-10
X	EP 0 855 999 A (JANSSEN PHARMACEUTICA NV) 5 August 1998 (1998-08-05) claim 1	1-10
X	WO 97 24324 A (JANSSEN PHARMACEUTICA NV; JANSSENS FRANS EDUARD (BE); SOMMEN FRANC) 10 July 1997 (1997-07-10) claim 1	1-10
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the International filing date but later than the priority date claimed

- 'T' later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- '&' document member of the same patent family

Date of the actual completion of the International search

12 November 2002

Date of mailing of the International search report

26/11/2002

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Fax: (+31-70) 340-3016

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Baston, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/27389

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 151 824 A (JANSSEN PHARMACEUTICA NV) 21 August 1985 (1985-08-21) claim 1	1-10
X	WO 01 30348 A (JANSSENS FRANS EDUARD ; JANSSEN PHARMACEUTICA NV (BE); DUGOVIC CHRI) 3 May 2001 (2001-05-03) claim 1	1-10
P,X	WO 01 77101 A (RIGBY AARON ; LAWRENCE LOUISE (GB); SANGANEE HITESH (GB); SPRINGTHO) 18 October 2001 (2001-10-18) claim 1	1-20
E	WO 02 081449 A (NOVARTIS ERFIND VERWALT GMBH ; ALBERT RAINER (CH); NOVARTIS AG (CH)) 17 October 2002 (2002-10-17) Examples 1-83 claim 1	1-20
P,X	PALANI, A. ET AL.: "Discovery of 4-'(Z)-(4-Bromophenyl)-(ethoxyimino)methyl !-1-'(2,4-dimethyl-3-pyridinyl)carbonyl!-4'-methyl-1,4'-bipiperidine N-Oxide (SCH 351125): An Orally Bioavailable Human CCR5 Antagonist for the Treatment of HIV Infection" JOURNAL OF MEDICINAL CHEMISTRY, vol. 44, no. 21, 11 October 2001 (2001-10-11), pages 3339-3342, XP002220286 example 13; table 1	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/27389

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9801425	A 15-01-1998		AU 728592 B2 AU 3581097 A CA 2259655 A1 EP 0912515 A1 HU 9904622 A2 JP 3068206 B2 JP 11514671 T NZ 333513 A WO 9801425 A1	11-01-2001 02-02-1998 15-01-1998 06-05-1999 28-06-2000 24-07-2000 14-12-1999 28-04-2000 15-01-1998
US 5952349	A 14-09-1999		NONE	
EP 0855999	A 05-08-1998		EP 0855999 A1 SI 855999 T1 AT 206397 T AU 707037 B2 AU 1308497 A BR 9612334 A DE 69615700 D1 DE 69615700 T2 DK 855999 T3 EA 1559 B1 HU 9904125 A2 JP 2000502690 T NO 982404 A NZ 325843 A PL 327441 A1 SK 83198 A3 US 6169097 B1 CA 2238818 A1 CZ 9801864 A3 WO 9724324 A1 ES 2164939 T3 PT 855999 T TR 9801211 T2 US 6346540 B1 ZA 9610885 A	05-08-1998 31-12-2001 15-10-2001 01-07-1999 28-07-1997 02-03-1999 08-11-2001 05-09-2002 21-01-2002 23-04-2001 28-06-2000 07-03-2000 19-08-1998 28-05-1999 07-12-1998 11-02-1999 02-01-2001 10-07-1997 16-12-1998 10-07-1997 01-03-2002 28-03-2002 21-09-1998 12-02-2002 23-06-1998
WO 9724324	A 10-07-1997		AT 206397 T AU 707037 B2 AU 1308497 A BR 9612334 A CA 2238818 A1 CZ 9801864 A3 DE 69615700 D1 DE 69615700 T2 DK 855999 T3 EA 1559 B1 WO 9724324 A1 EP 0855999 A1 ES 2164939 T3 HU 9904125 A2 JP 2000502690 T NO 982404 A NZ 325843 A PL 327441 A1 PT 855999 T SI 855999 T1	15-10-2001 01-07-1999 28-07-1997 02-03-1999 10-07-1997 16-12-1998 08-11-2001 05-09-2002 21-01-2002 23-04-2001 10-07-1997 05-08-1998 01-03-2002 28-06-2000 07-03-2000 19-08-1998 28-05-1999 07-12-1998 28-03-2002 31-12-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/27389

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9724324	A		SK 83198 A3 TR 9801211 T2 US 6169097 B1 US 6346540 B1 ZA 9610885 A	11-02-1999 21-09-1998 02-01-2001 12-02-2002 23-06-1998
EP 0151824	A 21-08-1985		US 4588722 A AT 51621 T AU 575612 B2 AU 3736385 A BG 47033 A3 CA 1246070 A1 DE 3481841 D1 DK 8885 A EP 0151824 A2 ES 539266 D0 ES 8604203 A1 FI 850078 A ,B, GR 850059 A1 HU 37780 A2 IE 57968 B1 IL 74017 A JP 60174778 A KR 8701046 B1 NO 850084 A NO 892563 A NZ 210675 A PH 21554 A PL 251476 A2 PT 79808 A ,B RO 91075 A1 SU 1400509 A3 ZA 8500186 A ZM 385 A1 ZW 585 A1	13-05-1986 15-04-1990 04-08-1988 01-08-1985 16-04-1990 06-12-1988 10-05-1990 10-07-1985 21-08-1985 16-01-1986 01-06-1986 10-07-1985 11-01-1985 28-02-1986 03-06-1993 31-03-1988 09-09-1985 26-05-1987 10-07-1985 10-07-1985 29-05-1987 11-12-1987 17-12-1985 01-02-1985 27-02-1987 30-05-1988 27-08-1986 29-08-1986 30-07-1986
WO 0130348	A 03-05-2001		AU 7788500 A WO 0130348 A1	08-05-2001 03-05-2001
WO 0177101	A 18-10-2001		AU 4699701 A WO 0177101 A1 US 2002077337 A1	23-10-2001 18-10-2001 20-06-2002
WO 02081449	A 17-10-2002	WO	02081449 A1	17-10-2002